

The Risk for Fatal Pulmonary Embolism after Discontinuing Anticoagulant Therapy for Venous Thromboembolism

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Background: The long-term risk for fatal pulmonary embolism (PE) after treatment of venous thromboembolism (VTE) may be an important factor in the decision to discontinue this treatment.

Objective: To provide reliable and precise estimates of the annual risk for fatal PE and the case-fatality rate of disease recurrence and to assess these outcomes according to the initial presentation of VTE (deep venous thrombosis [DVT], PE, or both) and its etiology (secondary or idiopathic) in patients who have discontinued anti-coagulant therapy.

Design: Prospective cohort study.

Setting: Academic medical centers.

Patients: Inception cohort of patients with a first episode of symptomatic VTE who discontinued anticoagulant therapy.

Measurements: Incidence rates of any fatal PE (which included sudden death from possible fatal PE) and definite or probable PE per 100 person-years of follow-up and case-fatality rate of recurrent VTE.

Results: Of 2052 patients studied, 1450 had DVT, 310 had PE, and 292 had DVT and PE. The mean duration of previous anti-

coagulant therapy was 6 months (range, 3 to 39 months), and the mean duration of follow-up after discontinuation of treatment was 54 months (range, 1 to 120 months). The annual risk for any fatal PE and definite or probable fatal PE after discontinuation of anticoagulation was 0.49 events (95% CI, 0.36 to 0.64 events) per 100 person-years and 0.19 events (CI, 0.12 to 0.30 events) per 100 person-years, respectively. The case-fatality rate of recurrent disease was 9.0% (CI, 6.8% to 11.8%) for any fatal PE and 3.8% (CI, 2.4% to 5.9%) for definite or probable fatal PE.

Limitation: The findings are less pertinent to patients with active cancer, permanent immobility, or high-risk thrombophilia.

Conclusion: The risk for fatal PE is 0.19 to 0.49 events per 100 person-years for patients who have finished a course of anticoagulant therapy for a first episode of symptomatic VTE. The case-fatality rate for death from recurrent PE is 4% to 9%. This information helps to inform patient prognosis and may assist clinicians in deciding whether to discontinue anticoagulant therapy for VTE.

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When deciding whether to discontinue anticoagulant therapy for venous thromboembolism (VTE), the subsequent risk for fatal pulmonary embolism (PE) is an important prognostic consideration. This risk can be expressed in absolute terms as the annual risk for fatal PE and in conditional terms as the risk that recurrent disease will be fatal (case-fatality rate) (1, 2). Knowledge of the annual risk for fatal PE may influence decisions about discontinuing anticoagulation, depending on the comfort level of clinicians and patients about an acceptably low risk for fatal PE. The case-fatality rate measures the clinical impact of disease recurrence if anticoagulation is discontinued, which can be weighed against the case-fatality rate of bleeding if anticoagulation is continued (3, 4).

Past studies do not adequately address these issues. They include meta-analyses, which are retrospective and

potentially unreliable (2); patient registry or population-based cohort studies that did not standardize anticoagulant therapy (5–9); or studies from linked administrative databases, which rely on secondary data sources that may be inaccurate (10–12). Furthermore, these studies did not monitor patients for recurrent disease for long enough (usually ≤ 1 year) to assess long-term risk for fatal PE. Finally, these studies provide limited data on the risk for fatal PE after anticoagulation is discontinued in patient subgroups, such as persons presenting with PE or idiopathic VTE (2, 5–12).

Therefore, we studied an inception cohort of patients who, after a first episode of VTE, had discontinued anticoagulant therapy and underwent clinical follow-up. We created the inception cohort by pooling data from 2 source studies (13–15). Our objective was to provide reliable and precise estimates of the annual risk for fatal PE and the case-fatality rate of recurrent PE. We also assessed these outcomes according to patients' initial presentation (deep venous thrombosis [DVT], PE, or both) and VTE etiology (secondary or idiopathic).

METHODS

Inception Cohort

We studied an inception cohort of patients who completed at least 3 months of anticoagulant therapy after a first episode of symptomatic VTE. The observation period

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for the inception cohort began when the patient discontinued anticoagulant therapy, and it ended when the patient had nonfatal DVT or PE, fatal PE, or death from another cause. If 1 of these outcomes did not occur, patients were observed until the study ended or for a maximum of 120 months, whichever came first.

Inception Cohort Subgroups

We placed patients in subgroups according to initial presentation of VTE (DVT alone, PE alone, or DVT and PE) and VTE etiology (secondary or idiopathic). We defined secondary VTE as occurring in the presence of 1 or more transient risk factors, such as surgery, leg trauma, leg fracture, or childbirth (within 3 months of presentation), or if the patient was bedridden for more than 1 week because of a medical illness, rheumatologic illness, pregnancy, or hormonal therapy use. We defined idiopathic VTE as occurring in the absence of any of the aforementioned risk factors.

Clinical Outcomes

During follow-up of the inception cohort, we assessed the following outcomes: recurrent nonfatal DVT (defined as a new noncompressible vein segment, an increase of the vein diameter by >4 mm compared with the last available measurement on venous ultrasonography, or a new intraluminal filling defect on venography); recurrent nonfatal PE (defined as a new ventilation–perfusion mismatch on lung scan or a new intraluminal filling defect on spiral computed tomography of the chest); definite or probable fatal PE; and possible fatal PE (sudden death of undetermined cause). We determined a cause of death for all deceased patients on the basis of autopsy records, hospital death certificates, and national death registries.

The diagnosis of fatal PE may be inaccurate because of bias from diagnostic suspicion about the cause of death in patients with previous VTE (16, 17). Therefore, we attempted to provide a more robust assessment of the annual risk for fatal PE by classifying fatal PE as “definite or probable” fatal PE or as “any” fatal PE (definite or probable PE and possible PE). A fatal PE was adjudicated as “definite” if it was confirmed at autopsy, “probable” if it was preceded in the immediate period before death by confirmed nonfatal PE or DVT, and “possible” if sudden death occurred that could not be explained by a disease or a condition other than PE.

Patients who had recurrent nonfatal VTE did not have further follow-up as part of our inception cohort because these patients would typically resume anticoagulation, which would make them ineligible for the inception cohort, and we had defined this cohort as no longer receiving anticoagulation.

Source Studies for Derivation of the Inception Cohort

The inception cohort was derived from the pooled patient populations of 2 source studies: a prospective co-

Context

The decision to discontinue anticoagulation for venous thromboembolism (VTE) should depend in part on the subsequent risk for a fatal recurrence. Previous studies have measured fatality rates in patients still receiving anticoagulant drugs.

Contribution

In a cohort from 2 source studies that had monitored 2052 patients for an average of 4.5 years after discontinuing anticoagulation for a first episode of VTE, the annual risk for any fatal pulmonary embolism (PE) was 0.43 events per 100 patient-years. The risk for definite or probable fatal recurrent PE was 0.17 events per 100 patient-years.

Implication

Although these rates seem low, decision makers must also take into account the rates of fatal PE recurrence and fatal hemorrhage if anticoagulant therapy is continued.

—The Editors

hort study of patients with VTE who received at least 3 months of anticoagulant therapy (13) and an open-label randomized trial that compared 6 weeks and 6 months of anticoagulant therapy in patients with VTE (14, 15). We included patients from the randomized trial only if they had been in the study arm that was randomly assigned to receive 6 months of anticoagulation because 6 weeks is less than the recommended duration of treatment for VTE (18). Although the inception cohort was derived from 2 patient populations, the source studies had common characteristics that allowed pooling of the populations into 1 homogeneous inception cohort. We describe these characteristics, common to both source studies, below.

Patient Characteristics

In both studies, the study population consisted of consecutive patients presenting with a first episode of symptomatic lower-limb DVT, PE, or both (patients with asymptomatic VTE were excluded) who were referred by a primary care physician (from a family practice or emergency department). Both studies excluded patients if they had at least 1 of the following conditions that would typically warrant lifelong anticoagulation: active cancer, permanent immobility, or high-risk thrombophilia.

Diagnosis of DVT and PE

Deep venous thrombosis and PE were confirmed by objective diagnostic testing in all patients in both studies. In the cohort study, all patients with DVT had venous ultrasonography–confirmed proximal DVT, and proximal DVT was defined as DVT involving the popliteal or more proximal deep vein segments. In the randomized trial, patients with DVT had venography–confirmed proximal or

distal (calf) DVT, depending on whether the thrombus was proximal or distal to the knee joint. Thus, patients with DVT in the popliteal vein (all of whom would have been classified as having proximal DVT by the cohort study criteria) had proximal DVT if the thrombosed vein segment was above the knee joint and distal DVT if the thrombosed vein segment was below the knee joint.

Anticoagulant Therapy

All patients in both studies received 5 to 10 days of unfractionated or low-molecular-weight heparin followed by a vitamin K antagonist, administered to achieve an international normalized ratio of 2.0 to 3.0. In the cohort study, therapy was given for at least 3 months but was left to the discretion of the treating physician in all other regards. Patients with secondary VTE typically received 3 to 6 months of anticoagulation, and patients with idiopathic VTE typically received 6 months or more of treatment. In the randomized trial, anticoagulant therapy was given for 6 weeks or 6 months, but we included only patients allocated to receive 6 months of treatment.

Follow-up after Discontinuing Anticoagulant Therapy

In both source studies, the authors followed patients for a prespecified period unless a patient died or was lost to follow-up. The length of patient follow-up differed according to the source study. In the cohort study, the follow-up protocol was a clinic visit or telephone call every 6 months after stopping anticoagulation until the study was completed or for a maximum of 120 months after discontinuation of anticoagulant therapy. The protocol for the randomized trial was a clinic visit at 3 and 6 months during the first year after discontinuation of anticoagulant therapy, and every 12 months thereafter for a maximum of 120 months after anticoagulant therapy was discontinued.

Assessment of Clinical Outcomes

Both source studies had independent adjudication committees that reviewed all clinical outcomes. The adjudication committee members in both source studies were unaware of patients' clinical characteristics at presentation or their treatment.

Statistical Analysis

We obtained the data sets from both source studies and combined them into a single data set so that we could perform a patient-level analysis of the outcomes of interest.

We used mean values and ranges to describe the clinical characteristics of patients at the time of initial presentation, when DVT or PE was diagnosed. We characterized anticoagulant therapy as the duration of treatment in months (mean and range) and as the proportion of patients who received therapy for 3 months, more than 3 months to 6 months, more than 6 months to 12 months, or more than 12 months. We described the duration of follow-up after anticoagulation was discontinued in months (mean

and range) and as the proportion of patients who had follow-up for 12 months or less, more than 12 months to 24 months, more than 24 months to 48 months, more than 48 months to 72 months, and more than 72 months. We described clinical outcomes that occurred during follow-up from the time that anticoagulation was discontinued until death or the end of patient follow-up.

To standardize for different lengths of follow-up in the inception cohort, we used the annual risk for any fatal PE and definite or probable fatal PE (the number of events per 100 person-years of follow-up). We measured the annual risk for fatal PE for all patients and in subgroups based on VTE presentation (DVT, PE, or both) and its cause (secondary or idiopathic). We defined the case-fatality rate as the proportion of recurrent venous thromboembolic events that were fatal. The case-fatality rate for any fatal PE was calculated as follows: any fatal PE \div (any fatal PE + any nonfatal VTE). The case-fatality rate for definite or probable fatal PE was calculated as follows: definite or probable fatal PE \div (definite or probable fatal PE + any nonfatal VTE).

We used the Kaplan–Meier method to determine the time course of events after anticoagulation was discontinued for patients with any fatal PE. To identify predictors for any fatal PE, we considered a priori the following variables, all of which were present at initial presentation: age (10-year increments), sex, initial disease presentation (DVT, PE, or both), cause of VTE (idiopathic or secondary), duration of anticoagulation (expressed in 1-month increments or as 3 months, >3 months to 6 months, >6 months to 12 months, and >12 months), and source study type (cohort or randomized trial). The ratio of putative predictors to outcomes (5:45) is considered adequate to provide stable estimates of regression coefficients in regression analyses (19). We used Cox multivariable regression analysis to assess an association between the predictor variables and the risk for any fatal PE. After backward modeling, only variables for which *P* was less than 0.10 were retained in the final model. We estimated the hazard ratio (HR) for any fatal PE and corresponding 95% CIs for each risk factor in the regression model. All *P* values were 2-sided. We used SAS software, version 8.2 (SAS Institute, Cary, North Carolina).

Role of the Funding Source

The study did not receive funding.

RESULTS

Inception Cohort Characteristics, Follow-up, and Outcomes

The inception cohort consisted of 2052 patients, of whom 1628 (79%) were derived from the source cohort study (13) and 424 (21%) from the source randomized trial (14, 15). **Table 1** shows patient characteristics at entry into the inception cohort for all patients and separately according to each source study. The mean duration of anti-

Table 1. Inception Cohort Characteristics*

Characteristic	All Patients	Patients Derived from Cohort Study	Patients Derived from Randomized Trial
Patients, <i>n</i>	2052	1628	424
Mean age (range), <i>y</i>	62 (16–96)	62 (16–96)	61 (18–91)
Women, <i>n</i> (%)	1082 (53)	893 (55)	189 (45)
Mean duration of previous anticoagulant therapy (range), <i>mo</i>	6 (3–39)	6 (3–39)	6 (6–6)
Duration of previous anticoagulant therapy, <i>n</i> (%)			
3 mo	540 (26)	540 (33)	NA
>3 to 6 mo	1241 (60)	817 (50)	424 (60)†
>6 to 12 mo	191 (9)	191 (12)	NA
>12 mo	80 (4)	80 (5)	NA
Mean duration of follow-up after stopping anticoagulation (range), <i>mo</i>	54 (1–120)	48 (2–120)	79 (1–120)
Patients who had follow-up, <i>n</i> (%)			
≤12 mo	211 (10)	168 (10)	43 (10)
>12 to 24 mo	335 (16)	305 (19)	30 (7)
>24 to 48 mo	517 (25)	471 (29)	46 (11)
>48 to 72 mo	434 (21)	395 (24)	39 (9)
>72 mo	555 (27)	289 (18)	266 (63)
Thrombophilia, <i>n</i> (%)‡			
Present	295 (14)	231 (14)	64 (15)
Absent	726 (35)	726 (45)	360 (85)
Not investigated	1031 (50)	671 (41)	0 (0)
Initial disease presentation, <i>n</i> (%)			
DVT alone§	1450 (71)	1075 (66)	375 (88)
Pulmonary embolism alone	310 (15)	261 (16)	49 (12)
DVT and pulmonary embolism	292 (14)	292 (18)	0 (0)
Patients with idiopathic VTE, <i>n</i> (%)	1138 (55)	866 (53)	272 (64)
Patients with secondary VTE and associated risk factors, <i>n</i> (%)			
All patients	914 (45)	762 (47)	152 (36)
Recent lower-limb trauma or fracture	312 (34)	312 (41)	NA
Recent surgery	311 (34)	311 (41)	NA
Estrogen-containing hormonal therapy¶	89 (10)	89 (12)	NA
Bedridden for >1 wk because of medical illness¶	69 (8)	69 (9)	NA
Pregnancy¶	29 (3)	29 (4)	NA
Rheumatologic illness¶	14 (2)	14 (2)	NA
Recent childbirth	10 (1)	10 (1)	NA
Deaths (all-cause), <i>n</i> (%)	278 (14)	160 (10)	118 (28)
Patients lost to follow-up after anticoagulant therapy stopped or resumed anticoagulation for reasons other than recurrent VTE, <i>n</i> (%)	44 (2)	32 (2)	12 (3)
Clinical outcomes occurring during follow-up, <i>n</i> (%)			
All events	501 (24)	374 (23)	127 (30)
Nonfatal DVT	340 (68)	241 (64)	99 (78)
Nonfatal pulmonary embolism	116 (23)	95 (25)	21 (17)
Possible fatal pulmonary embolism (undetermined cause of sudden death)	27 (5)	27 (7)	0 (0)
Definite or probable fatal pulmonary embolism	18 (4)	11 (3)	7 (6)

* DVT = deep venous thrombosis; NA = not available; VTE = venous thromboembolism.

† All patients in this study received 6 months of anticoagulant therapy.

‡ Defined as ≥1 of the following: factor V Leiden mutation; prothrombin mutation; deficiency of protein C, protein S, or antithrombin; or antiphospholipid antibody.

§ Included 159 patients with distal DVT; patients may have had >1 risk factor.

|| Within 3 months.

¶ At initial presentation.

coagulation before inception cohort entry was 6 months (range, 3 to 39 months), and 96% of patients received between 3 and 12 months of anticoagulant therapy.

The mean duration of follow-up of the inception cohort after discontinuation of anticoagulant therapy was 54 months (range, 1 to 120 months). Five hundred one (24%) patients had a clinical outcome of interest during follow-up: 340 episodes of DVT, 116 episodes of nonfatal PE, 27 episodes of possible fatal PE (an undetermined cause of sudden death), and 18 episodes of definite or

probable fatal PE. Two hundred seventy-eight (14%) patients died of any cause. Forty-four (2%) patients were lost to follow-up or resumed anticoagulant therapy for reasons other than recurrent VTE. For these patients, follow-up ended at the time of last contact or on resuming anticoagulant therapy.

Risk for Fatal PE

Table 2 shows the annual risk for any fatal PE and definite or probable fatal PE for all patients and for sub-

Table 2. Risk for Fatal Pulmonary Embolism after Discontinuing Anticoagulant Therapy*

Patient Group	Person-Years of Follow-up	Fatal PE Events per 100 Person-Years of Follow-up			
		Any Fatal PE†		Definite or Probable Fatal PE	
		Events, n	Risk Estimate (95% CI)	Events, n	Risk Estimate (95% CI)
All patients (n = 2052)	9257	45	0.49 (0.36–0.64)	18	0.19 (0.12–0.30)
Initial disease presentation					
DVT (n = 1450)	6820	31	0.46 (0.32–0.64)	13	0.19 (0.11–0.32)
PE (n = 310)	1297	7	0.54 (0.24–1.07)	3	0.23 (0.06–0.63)
DVT and PE (n = 292)	1140	7	0.61 (0.27–1.22)	2	0.18 (0.03–0.58)
Cause of disease					
Idiopathic (n = 1138)	4844	35	0.72 (0.51–0.99)	12	0.25 (0.13–0.42)
Secondary (n = 914)	4413	10	0.23 (0.12–0.40)	6	0.14 (0.06–0.28)

* DVT = deep venous thrombosis; PE = pulmonary embolism.
 † Consists of definite or probable fatal PE plus possible fatal PE (undetermined cause of sudden death).

groups of patients classified according to initial VTE presentation and VTE etiology. The annual risk for fatal PE was 0.49 events per 100 person-years for any fatal PE and 0.19 events per 100 person-years for definite or probable fatal PE.

Case-Fatality Rate of Disease Recurrence

Table 3 shows the case-fatality rate of disease recurrence for all patients and for inception cohort subgroups. The case-fatality rate of disease recurrence for patients who initially presented with DVT, PE, or both was 8.5%, 12.3%, and 8.9%, respectively, for any fatal PE and 3.8%, 5.7%, and 2.7%, respectively, for definite or probable fatal PE.

Secondary Analyses

Figures 1 and 2 show the time course of fatal PE after discontinuation of anticoagulant therapy, according to initial VTE presentation and VTE etiology. Cases of fatal PE seemed to cluster over time. During the first year after

anticoagulant therapy was discontinued, the incidence of any fatal PE and definite or probable fatal PE was 0.81% (95% CI, 0.48% to 1.28%) and 0.35% (CI, 0.15% to 0.70%), respectively. After the first year, the annual risk for any fatal PE and definite or probable fatal PE was 0.40 (CI, 0.27 to 0.57) and 0.15 (CI, 0.08 to 0.26) events per 100 person-years, respectively. In the regression analysis, increasing age (HR, 2.12 [CI, 1.58 to 2.81]; *P* < 0.001) and idiopathic VTE (HR, 2.42 [CI, 1.20 to 4.90]; *P* = 0.014) were associated with an increased risk for any fatal PE (Table 4). Disease presentation (DVT or PE) did not affect the risk for fatal PE.

DISCUSSION

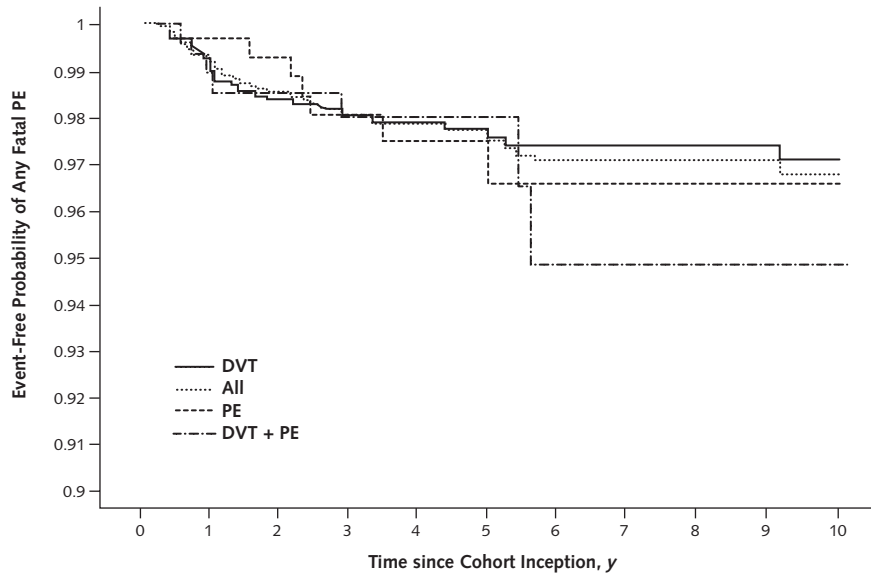
We aimed to provide reliable and precise estimates of the annual risk for fatal PE and the case-fatality rate of recurrent disease after discontinuation of anticoagulant

Table 3. Case-Fatality Rate of Recurrent Venous Thromboembolism after Discontinuing Anticoagulant Therapy*

Patient Group	Case-Fatality Rate			
	Based on Any Fatal PE†		Based on Definite or Probable Fatal PE‡	
	Estimate (95% CI)	Fatal Events/ All Events, n/n	Estimate (95% CI)	Fatal Events/ All Events, n/n
All patients	9.0 (6.8–11.8)	45/501	3.8 (2.4–5.9)	18/474
Initial disease presentation				
DVT	8.5 (6.1–11.8)	31/365	3.8 (2.2–6.3)	13/347
PE	12.3 (6.1–23.3)	7/57	5.7 (1.9–15.4)	3/53
DVT and PE	8.9 (4.4–17.1)	7/79	2.7 (0.7–9.3)	2/74
Cause of disease				
Idiopathic	9.8 (7.1–13.3)	35/358	3.6 (2.1–6.2)	12/335
Secondary	7.0 (3.8–12.4)	10/143	4.3 (2.0–9.1)	6/139

* DVT = deep venous thrombosis; PE = pulmonary embolism.
 † Any fatal PE divided by any fatal PE plus nonfatal venous thromboembolism.
 ‡ Probable or definite fatal PE divided by probable or definite fatal PE plus nonfatal venous thromboembolism.

Figure 1. Time course of any fatal pulmonary embolism (PE) after discontinuing anticoagulant therapy, according to the cause of venous thromboembolism.



Patients at risk, <i>n</i>	0	1	2	3	4	5	6	7	8	9	10
All	2052	1907	1555	1304	1036	793	569	468	395	330	90
DVT only	1450	1348	1096	946	762	600	453	378	322	272	68
DVT + PE	292	269	213	168	129	90	50	40	31	23	16
PE only	310	290	246	190	145	103	66	50	42	35	6

DVT = deep venous thrombosis.

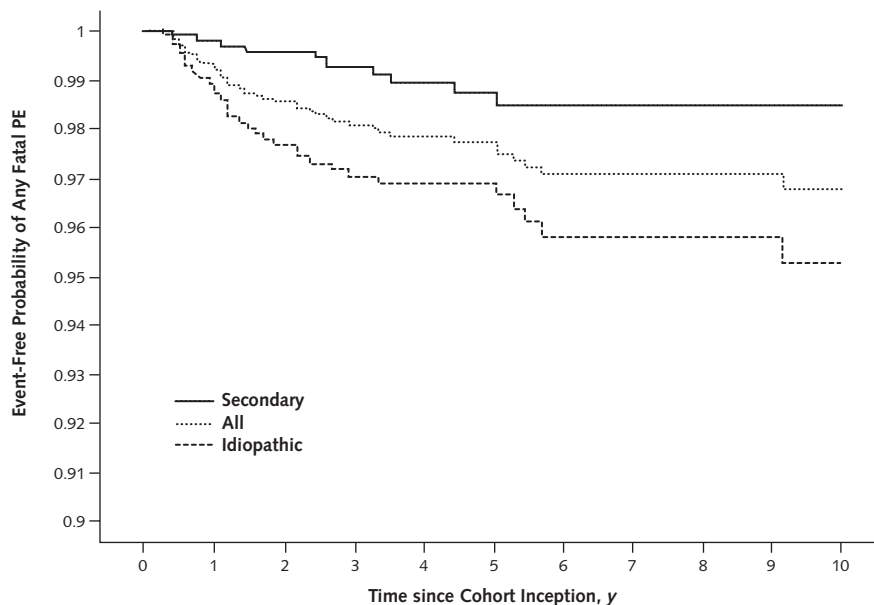
therapy for a first episode of symptomatic VTE. Our data are based on an inception cohort of more than 2000 patients who were followed, on average, for 4.5 years after discontinuing anticoagulant therapy. We found that the risk for death from PE after stopping anticoagulation is 0.19 to 0.49 events per 100 person-years and the case-fatality rate of recurrent VTE is 4% to 9%. The lower bounds of these estimates correspond to a rigorous definition of fatal PE. The upper bound includes difficult-to-confirm cases of possible fatal PE.

We believe our findings are valid on the basis of several considerations. First, the study population was well defined and homogenous in that all patients had a first episode of symptomatic VTE; received similar initial anticoagulation; and completed, on average, 6 months of oral anticoagulant therapy. Second, we defined the observation period uniformly as the interval between discontinuation of anticoagulation and occurrence of a clinical outcome. Third, all patients had careful follow-up, making it likely that we identified all outcome events. Finally, all nonfatal outcomes were confirmed by objective diagnostic tests. We did not have autopsy confirmation of all PE deaths, which is unrealistic given the marked decline in autopsy rates (20, 21). We therefore prespecified separate analyses for patients with any fatal PE (including those with possible fatal PE) and for patients with definite or probable fatal PE (those with autopsy-confirmed fatal PE or those with antecedent

clinical features of recurrent VTE). Consequently, our risk estimates for fatal PE and case fatality of recurrent VTE encompass a range of values. The true annual risk for fatal PE and case-fatality rate of recurrent disease probably lie between our maximum point estimates (based on any fatal PE) and minimum point estimates (based on definite or probable fatal PE).

Our findings can be applied to advise patients with a first symptomatic VTE about their prognosis after discontinuing anticoagulation. They are less pertinent to patients with active cancer, permanent immobility, or high-risk thrombophilia, who were not part of our inception cohort and typically receive lifelong anticoagulation (18). Our reported rates of fatal PE may reassure patients that their prognosis is good after stopping anticoagulation, with a low (<1% per year) risk for future fatal PE that is further reduced if the initial VTE after exposure to a transient risk factor or if they have discontinued anticoagulants for more than 1 year. Our findings may also help clinicians to decide whether anticoagulant therapy should be continued or stopped, especially in patients with idiopathic VTE, in whom the ideal duration of treatment is not well defined (18). For example, the annual risk for disease recurrence if anticoagulation is discontinued is about 10% (22) among patients with a first idiopathic VTE, and the annual risk for major bleeding if anticoagulation is continued is about 2% (23). When we consider our 4% to 9% case-fatality

Figure 2. Time course of any fatal pulmonary embolism after discontinuing anticoagulant therapy, according to the cause of venous thromboembolism.



Patients at risk, <i>n</i>	0	1	2	3	4	5	6	7	8	9	10
All	2052	1907	1555	1304	1036	793	569	468	395	330	90
Idiopathic	1138	1038	816	665	537	415	291	234	199	166	39
Secondary	914	869	739	639	499	378	278	234	196	164	51

rate of recurrent VTE, coupled with the 8% to 9% case-fatality rate of anticoagulant-related bleeding (3, 24), the balance of risks seems to favor continuing anticoagulant therapy. Thus, the annual risk for death from bleeding if anticoagulation is continued is 0.16% to 0.18% (2% bleeding risk \times 8% to 9% case-fatality rate), whereas the annual risk for death from recurrent VTE if anticoagula-

tion is discontinued is 0.40% to 0.90% (10% recurrence risk \times 4% to 9% case-fatality rate). However, because the absolute difference in risk for death with either approach is small, other individual patient factors may be considered in decisions about whether to continue or stop anticoagulation. These include D-dimer levels after discontinuing anticoagulant therapy (25), the estimated risk for nonfatal

Table 4. Risk Factors for Any Fatal Pulmonary Embolism after Discontinuing Anticoagulant Therapy*

Risk Factor	Hazard Ratio (95% CI)	P Value
Univariable regression analysis		
Age (10-year increments)	2.12 (1.60–2.81)	<0.001
Sex (male vs. female)	1.28 (0.71–2.30)	0.41
Disease etiology (idiopathic vs. secondary)	3.07 (1.52–6.21)	0.002
Treatment duration (1-month increments)	1.00 (0.94–1.07)	0.99
Treatment duration (vs. >12 months)		
3 months	0.46 (0.06–3.51)	0.45
>3 to 6 months	0.56 (0.08–4.13)	0.57
>6 to 12 months	0.30 (0.04–2.44)	0.26
Initial disease presentation (vs. PE)		
DVT	1.10 (0.48–2.49)	0.82
DVT and PE	0.89 (0.31–2.54)	0.83
Study type (randomized trial vs. cohort study)	0.54 (0.24–1.24)	0.15
Multivariable regression analysis		
Age (10-year increments)	2.12 (1.58–2.81)	<0.001
Disease etiology (idiopathic vs. secondary)	2.42 (1.20–4.90)	0.014

* DVT = deep venous thrombosis; PE = pulmonary embolism.

outcomes (for example, postthrombotic syndrome, chronic pulmonary hypertension) (26, 27), and patient preferences.

The focus of our study differs from that of the studies from which we formed our inception cohort. These studies focused on the incidence and predictors of nonfatal VTE (13–15), whereas we focused on the incidence of fatal PE and clinical impact of disease recurrence (case-fatality rate). Our findings extend our knowledge of the prognosis of patients with VTE in 2 ways. First, we focused on the risk for fatal PE and case-fatality rate of recurrent disease after anticoagulation is discontinued. Previous studies assessed these outcomes during the initial 3 months after diagnosis, when patients were still receiving anticoagulant therapy (5, 6), or they did not specify whether recurrent disease occurred during anticoagulation or after it was discontinued (7–12). Distinguishing between the risk for fatal PE after discontinuing anticoagulation and its risk during anticoagulation, especially during the first month after diagnosis (when most recurrences occur [28]), is clinically important because the difference between the risk for recurrence while on and off treatment is central to the decision about whether to continue or stop anticoagulation.

In addition, we assessed the risk for fatal PE and case-fatality rate of recurrent disease in patient subgroups, especially those with PE in whom data on the subsequent risk for fatal PE are limited (2, 8, 11). In our study, the case-fatality estimates of recurrent disease in patients who presented with PE (5.7% to 12.3%) seemed to be higher than those of patients who presented with DVT (3.8% to 8.5%) but were lower than those reported in a meta-analysis (24%) (2). These discrepant findings may be explained by differences in study methods. In the meta-analysis, the observation period began at the time of diagnosis and lasted until after anticoagulant therapy ended. Therefore, patients who had a fatal PE early in the course of their disease were counted in the case-fatality estimates. We did not count early deaths from PE because the observation period began after anticoagulant therapy was discontinued.

Our study has potential limitations. First, the duration of anticoagulant therapy was not standardized before entry into the inception cohort, which could affect the incidence of fatal PE after treatment was stopped. However, in pre-specified regression analyses, we found that the duration of anticoagulation, which ranged from 3 months to more than 12 months, did not affect the incidence of fatal PE after discontinuation of anticoagulant therapy (HR, 1.00 [CI, 0.94 to 1.07]). Furthermore, in accordance with current treatment recommendations (18), all patients received at least 3 months of anticoagulation, and those with idiopathic VTE received at least 6 months of treatment. Second, our inclusion of 159 patients with smaller (distal) DVTs might underestimate the risk for fatal PE. However, post hoc analysis showed that the annual risk for definite or probable fatal PE after discontinuation of anticoagulation was similar in patients with distal DVT (0.18% [CI, 0.03% to 0.58%]) and proximal DVT (0.19% [CI, 0.11%

to 0.30%]). Therefore, patients with distal DVT had clinically important DVT, and their inclusion in our study was justified. Third, our analysis to identify risk factors for fatal PE did not include patient comorbid conditions, such as cardiorespiratory diseases, in the regression models because the source studies did not collect this information. Such comorbid conditions might confer an increased risk for fatal PE (2) and, in addition, might have influenced the risk estimates for fatal PE with the observed predictor variables. Finally, although the source studies for the inception cohort differed in some methods, we believe that these differences, such as the frequency of patient follow-up, are unlikely to affect our rates of fatal recurrence. Furthermore, post hoc analysis showed the annual risk per 100 person-years for definite or probable fatal PE was similar in the cohort study (0.17 [CI, 0.09 to 0.30]) and the randomized trial (0.25 [CI, 0.11 to 0.50]).

To summarize, in patients with a first episode of symptomatic VTE who have discontinued anticoagulant therapy, the risk for fatal PE is 0.19 to 0.49 events per 100 person-years, and the case-fatality rate from recurrent PE is 4% to 9%. This information helps to inform patient prognosis and may assist clinicians in deciding whether to discontinue anticoagulant therapy after VTE.

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