# Death due to recurrent thromboembolism among younger healthier individuals hospitalized for idiopathic pulmonary embolism

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**Summary**

The incidence of death due to recurrent pulmonary embolism (PE) after a first-time idiopathic PE is not well defined. We conducted a retrospective study of patients age 18 to 56 years who had idiopathic PE between 1994–2001. The incidence and cause of death within five years was determined using linked discharge records and a master death registry. A total of 3,456 patients had a first-time idiopathic PE. The rate of recurrent VTE 0–6 months after the index event was 13.1%/year, and 2.9%/year 6–60 months after the event. During the mean follow-up of 3.2 years 118 (3.4%, 95% confidence interval [CI]=2.8–4.1%) patients died. Fifty-two (44%) deaths occurred <29 days after the index PE (case-fatality rate =1.5%, 95%CI=1.1–2.0%). Among the 66 cases (1.9%) that died after 28 days, 18 (0.52%) were due to recurrent PE or its sequelae: eight had recurrent PE alone, five had recurrent PE and a serious co-morbid illness, and five had thromboembolic pulmonary hypertension with or without acute PE. The person-time rate of death (deaths per 100 patient-years) attributed to any recurrent thromboembolism 6–60 months after the event was 0.16% (95%CI=0.1–0.26%). Ten of the 18 (56%) late thromboembolic deaths reflected a first-time recurrent PE. The 28-day case-fatality rate for recurrent VTE was 2.8% (95%CI= 1.5–4.9%). In this cohort of younger patients with idiopathic PE, the rate of death due to recurrent VTE, particularly to first-time recurrent PE, was low. Among the patients who died of thromboembolism >28 days after the index PE, 28% had developed pulmonary hypertension.

**Keywords**

Thromboembolism, epidemiology, PE, venous thrombosis, administrative data

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## Introduction

One of the most difficult questions that a clinician faces when treating a younger patient with idiopathic pulmonary embolism (PE) is whether to continue oral anticoagulation indefinitely or to discontinue therapy at the end of the three- to six-month treatment period that is generally recommended (1). A number of studies have addressed the decision making that is involved, and this process depends on an accurate estimation of five clinical outcomes: i) the risk of bleeding if anticoagulation therapy is continued, ii) the risk of recurrent venous thromboembolism (VTE) if anticoagulation is stopped, iii) the risk that a recurrent VTE will be manifest as PE versus deep vein thrombosis (DVT), iv) the morbidity of a recurrent DVT event, and v) the case-fatality rate of recurrent PE (2–4). Although prior studies have provided estimates of the incidence of the first four clinical outcomes, there is a paucity of reliable data regarding both the incidence and case-fatality rate of recurrent PE, particularly among generally healthy younger individuals who have few or no chronic co-morbid medical conditions

There is no perfect and unbiased method to accurately determine the incidence and case-fatality rate of recurrent PE in younger patients with idiopathic PE. Prospective cohorts (5), registries (6, 7), and clinical trials (8), are prone to various forms of case selection bias, particularly because they often exclude sicker patients and include only a small number of younger individuals. Observational studies frequently lack sufficient sample size or duration of follow-up, they may not be able to identify all

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the deaths (9, 10), and they may extend over such a long timeframe that there is significant variation in clinical practice (11). Perhaps the two most significant limitations to the studies that have been published to date are the absence of follow-up beyond the initial treatment period and the absence of information about the presence or absence of coexisting acute or chronic co-morbid disease (12–15). Douketis et al. recently reported the incidence of fatal PE in a cohort of 2,052 VTE patients treated with oral coagulants for an average of six months, but their cohort was older (mean age 62 years) and the majority (70%) were diagnosed with DVT alone, not PE (16).

The aim of the present study was to determine both the short-term (0–6 months) and long-term (>6 months) incidence death due to recurrent thromboembolic disease among younger "healthier" patients diagnosed with a first-time idiopathic PE. Although no information was available regarding chronic anticoagulation treatment, based on large cohort studies from the late 1990s we expected that fewer than 20% of cases would be expected to remain on oral anticoagulant therapy beyond 6–12 months. By focusing only on patients under the age of 56 years who had at most one co-morbid condition, we aimed to minimize the number of patients who had multiple chronic medical co-morbid conditions. By using the comprehensive linked California patient discharge data set linked to the state's master death registry, we identified all hospitalizations between the initial PE event and death, and determined the presence or absence of acute or chronic co-morbid illnesses.

## Methods

### Database

The California Patient Discharge Data Set has been described in detail in other manuscripts (17). All non-federal hospitals supply specific information about each inpatient, including basic demographic data, the principal diagnosis, up to 24 secondary diagnoses, a principal procedure, and up to 20 secondary procedures using *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) codes. Since July of 1990 the use of an encrypted record linkage number has allowed serial hospitalizations to be linked. Diagnoses are based on conditions listed by the physicians caring for the patient, and are not based on specific criteria. For example, a diagnosis of obesity is not based on the body mass index (BMI), but only the physician's written opinion. The study was approved by the California Health and Welfare Agency Committee for the Protection of Human Subjects, and the University of California, Davis Human Subjects Committee.

### Cohort first-time idiopathic PE

For inclusion, cases had to be 18 to 56 years old, have a principal diagnosis of PE (ICD-9-CM code, 415.1x), or a principal diagnosis of DVT (451.1x; 451.2; 451.81; 451.9; 453.1; 453.2; 453.8; and 453.9) *plus* a secondary diagnosis of PE, and be hospitalized between Jan 1,1994– Sept 30, 2001. To include only cases with a first-time PE, all cases that had a prior history of VTE (= specific codes) or the presence of a V12.51 or V12.52 code (past history of VTE) back to July 1, 1990 were excluded. Idiopathic PE was defined as a PE in the absence of a provoking risk factor, specifically: i) diagnosis of an active cancer (ICD-9-CM codes) within one year prior to admission or within four months following the date of admission (18), ii) a preceding medical or surgical hospitalization (including trauma) within three months, iii) a recent or ongoing pregnancy (no delivery of a newborn within 3 months prior to or 9 months following the day of admission) and iv) a diagnosis of chronic pulmonary hypertension or pulmonary heart disease (416.0, 416.8, 416.9) at the time of or prior to the index hospitalization. We assumed that in the late 1990s that all cases with acute PE would have been hospitalized for at least three days to receive parenteral anticoagulant therapy. Therefore, cases coded as having acute PE that were hospitalized for less than three days (unless the case died on hospital day 0, 1 or 2) were excluded because they more likely reflected a coding error than true PE. No specific information was available regarding the presence or absence of an underlying thrombophilic disorder.

### Recurrent thromboembolism

Recurrent VTE was defined as readmission to a hospital with a principal diagnosis of DVT or PE or sudden death outside the hospital that was adjudicated to be due to thromboembolism. Recurrent VTE events were classified in the same fashion as the index event, with cases coded as having only a DVT classified as having recurrent DVT whereas cases coded as having a PE alone or PE with DVT were classified as having a recurrent PE event. The number of cases that developed recurrent VTE during the index hospitalization could not be determined. Recurrent events occurring six or more months after the index event were labeled "long-term".

### Concurrent chronic medical co-morbidity

In order to assemble a sufficiently large study cohort, patients with one chronic co-morbidity were included, but to minimize the effect of multiple co-morbidities on the incidence of recurrent VTE (19), patients with more than one chronic co-morbidity were excluded. Presence of chronic medical co-morbidity was determined using a modification of the Healthcare Costs and Utilization Project (aka, 'Elixhauser index') co-morbidity software. 3.1 (Sept 2005 version) (20–22). Use of this co-morbidity index has been described in previous reports (19, 23). Information from the index hospital stay as well as any hospitalizations in the prior 12 months was used to define the presence of a co-morbid condition (24). In studies that analyzed the validity of co-morbidity data, misclassification was rare, and there was very good agreement between the administrative data and chart review data (22, 25).

### Bleeding

Major bleeding was defined as a hospital admission with a principal diagnosis of intraocular, intracranial, esophageal, gastric, gastrointestinal, renal, intra-articular, or pulmonary bleeding using specific ICD-9-CM codes (26). Hematuria was not included since most cases reflect minor bleeding.

### Deaths

Deaths were identified using the linked State of California Master death file, which identifies the cause of all deaths of California residents both within the state and outside of the state. The cause of death that is listed on the death certificate is determined

by the National Center for Health Statistics and mapped into an ICD-10 code. This data base includes a variable indicating if an autopsy was performed. The adjudicated cause of death for each case was determined by review of the death certificate cause of death coupled with a detailed analysis the terminal hospital discharge diagnoses and all prior hospital discharge diagnoses. Eighty percent of the deaths that occurred within the five-year follow-up period occurred in a hospital, allowing direct comparison of hospital diagnoses with the cause of death listed on the death certificate. Deaths were categorized as being caused by recurrent thromboembolism or unrelated to thromboembolism (e.g. admitted for acute myocardial infarction, death certificate listing acute infarction as cause of death). The thromboembolism deaths were classified as: i) due to acute recurrent PE alone (out-of-hospital death with PE listed as cause of death on the death certificate, or sudden unexplained death, or hospital admission for PE and death < 30 days), ii) due to recurrent PE coupled with a serious acute or chronic medical illness (admission for recurrent PE coupled with recurrent hospitalizations for a chronic illness such as human immunodeficiency virus (HIV), lupus erythematosus, etc., and iii) due to pulmonary hypertension diagnosed after recurrent PE, with or without a recurrent acute PE at the time of death.

Out-of-hospital deaths that had a death certificate diagnosis of cancer or a chronic medical problem that had been identified during a prior hospitalization, such as HIV or cardiomyopathy etc., were assumed to have died of the specified chronic disease. In order to avoid misclassifying any case that potentially died of acute recurrent PE, all cases that died out of hospital with a non-specific cause of death on the death certificate (such as 'atherosclerosis') that did not have an autopsy, and that had a cause of death that was not consistent with any prior medical diagnoses were assumed to have died of an acute PE. Two of the authors (RHW, SM) reviewed this information for all deaths, and assignment of the final adjudicated cause of death was determined by consensus. Deaths within 28 days of either the index or the recurrent VTE event were used to calculate the case-fatality rate.

### Statistics

All death rates were calculated as an incidence density in person-time, equal to the number of patients dying per 100 patients living one year, and expressed as the percent patients dying per year. Categorical data was analyzed using $Chi^2$-testing. Differences in person-time rates were compared using a two-tailed mid-P exact test. Confidence limits on rate data were computed using OpenEpi (27), Kaplan Meier methods were used to plot survival and incidence of recurrent VTE. Analyses were performed using SAS (version 9.2) and a two-sided p-value less than 0.05 was considered statistically significant.

## Results

During the study period, 10,629 cases were admitted to California hospitals for a first-time idiopathic PE. Of these cases, 3,456 satisfied the entrance criteria of being 55 years or younger and having at most just one chronic co-morbid medical condition. The demographic and clinical characteristics of this cohort are shown in Table 1. The frequency of the most common chronic co-

**Table 1: Demographic and clinical characteristics of the 3,456 cases with idiopathic pulmonary embolism (PE).**

| Variable | N (%) (n = 3,456) |
|---|---|
| Age, years ± SD | 41.9 ± 9.3 |
| Sex, N (%) female | 50% |
| Race, N (%) | |
| Caucasian | 2,520 (73%) |
| African American | 383 (11%) |
| Hispanic | 386 (11.1) |
| Asian | 6 (0.2%) |
| Other | 164 (4.7%) |
| One chronic co-morbid condition | 1,353 (39%) |
| Follow-up, mean | 3.2 years |
| Hospitalized for recurrent VTE, N (%)* | 441 (12.8%) |
| 0–182 days after index event | 204 (5.9%) |
| > 182 days-5 years | 237 (6.6%) |
| Rate of recurrent VTE (% = events/100 patient-years) | |
| 0–182 days | 13.1%/year |
| 183–5 years | 2.9%/year |
| Major bleeding < 5 years. N (%) | 280 (8.1%) |
| Death < 5 years | 118 (3.5%) |
| 0–182 days | 58 (1.7%) |
| 183 days- 5 years | 60 (1.8%) |
| Death rate (% = events/100 patient-years) | |
| 0–182 days | 3.7%/year |
| 183 days- 5 years | 0.72%/year |
| Death rate due to VTE (% = events/100 patient-year) | |
| 0–182 days | 3.2%/year |
| 183 days- 5 years | 0.16%/year |

* CI cumulative incidence, seven recurrent VTE cases died out-of-hospital.

**Table 2: Most common medical co-morbidities in the pulmonary embolism (PE) cohort.**

| Chronic medical co-morbidity* | Number of cases |
|---|---|
| Obesity | 250 |
| Hypertension | 220 |
| Chronic anemia | 179 |
| Asthma | 135 |
| Depression | 71 |
| Gastroesophogea reflux | 54 |
| Diabetes | 51 |
| Hypothyroidism | 45 |
| Sleep apnea | 44 |
| Human immunodeficiency virus infection | 24 |

* Does not necessarily correspond to Elixhauser co-morbidity categories; this is simply a list of the most common co-morbid conditions.

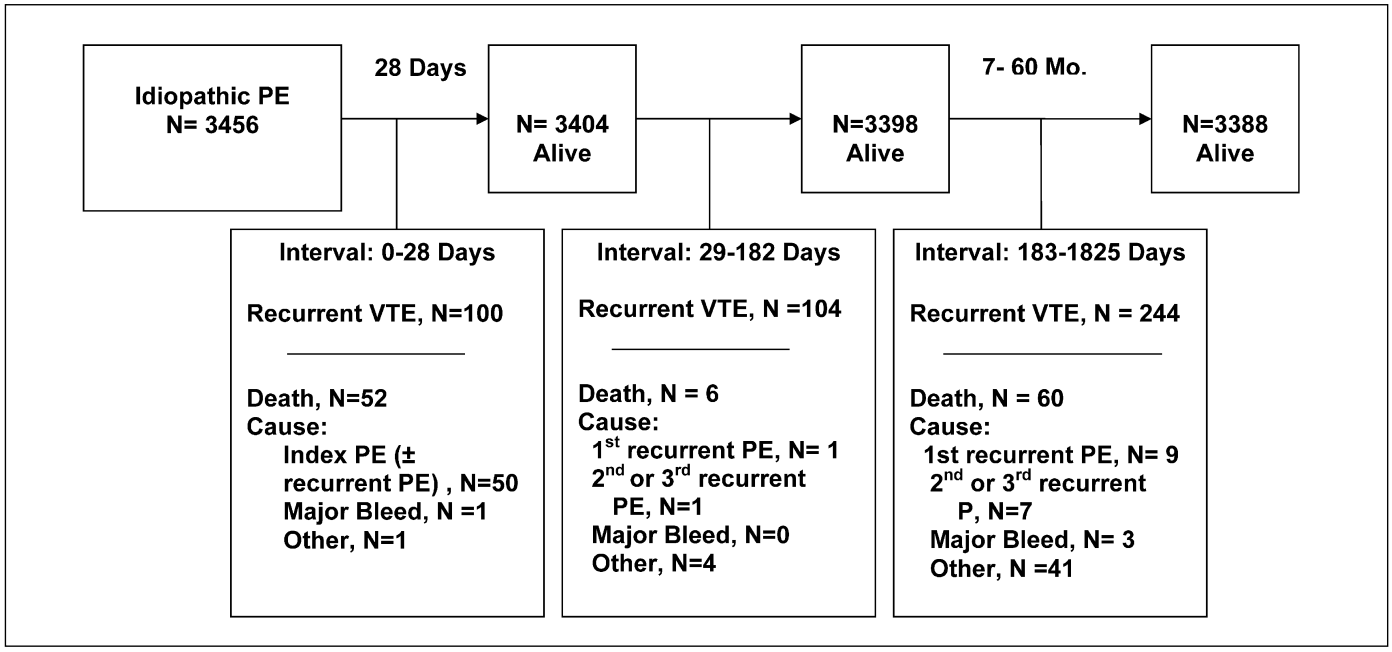


**Figure 1: Schematic diagram of deaths and recurrent PE events (recurrent PE) over the time of the study.**

morbidities that were present at the time of the index hospitalization is shown in Table 2. The mean age was 42 ± 9 years, 50% of the cases were men, 73% were Caucasian, and the mean follow-up time was 3.2 years (91 days- 5 years).

### Recurrent VTE events

There were a total of 448 (12%, CI=11.8%-14%) cases with recurrent VTE. Of these, 441 cases were hospitalized with a recurrent VTE, 68% were diagnosed as PE and 32% as DVT alone. Seven additional cases had recurrent PE but died out-of-hospital: five had a death certificate diagnosis of thromboembolism (n=5) and two were adjudicated to have died due to recurrent PE. The incidence of recurrent PE and death during the study period is depicted schematically in Figure 1. There were 100 (22%) cases with recurrent VTE during days 0–28, 104 (23%) between days 29 and 182 and 244 (54%) between six months and five years after the index event. The annualized rate (= events/100 patients/year) of recurrent VTE in months 0–6 months after the index event was 13.1% per year (CI=11.4%-15%) whereas from six months to five years the rate was 2.9% (CI=2.5–3.2%) per year. A Kaplan-Meier plot of the incidence of first-time recurrent PE events is shown in Figure 2.

### Deaths

During the study period 118 (3.4%, CI=2.8–4.1%) cases died and 40 of these cases underwent autopsy. A Kaplan-Meier plot of survival from the initial hospitalization for PE is shown in Figure 3. Fifty-two (43%) of the deaths occurred within 28 days of the index hospital admission for PE (case-fatality rate = 1.5%). Fifty-one of these deaths occurred during the index hospitalization, and 30 (58%) of these occurred on the first or second hospital day. Fifty of the 51 hospital deaths had PE listed as the cause of death on the death certificate diagnosis, and 25 of these had undergone autopsy. The remaining patient had mastoiditis listed as the cause of death, which occurred on the 6th hospital day. One patient died of major bleeding two days after hospital discharge. Of the 50 patients who died within 28 days and who had PE listed as the cause of death, 11 (22%) had a serious underlying medical illness (e.g. neuromuscular disease, sickle-cell disease, sepsis etc.), 24 (48%) had a chronic co-morbid conditions, and 17 (34%) had no other medical condition listed

Among the 66 (1.9%) later deaths that occurred 29 or more days after the index hospitalization, 18 were adjudicated as being caused by either recurrent PE alone (n=8), recurrent PE coupled with a significant underlying co-morbid condition (n=5), or recurrent PE leading to pulmonary hypertension, with death due to either a recurrent PE or heart failure (n=5). Death certificates listed thromboembolism as the cause of death in 14 of the 18 cases: six cases with PE, three cases with DVT and five cases with pulmonary hypertension. Five of the 18 cases had undergone autopsy. The four remaining cases that were classified as thromboembolic deaths had death certificate diagnoses of myocardial infarction, hypertension, uncomplicated diabetes and anoxic brain damage. These later four cases were adjudicated to be likely due to PE because they either died suddenly out of the hospital (n=2), presented with cardiac arrest (n=1), or were admitted to a hospital for recurrent PE and died within three days (n=1). None of these cases underwent autopsy. In 10 of the 18 (56%) late deaths attributed to recurrent thromboembolism, the death was associated with a first-time recurrent thromboembolic event, and seven of these cases died out-of-hospital, whereas three were admitted and died in-hospital. Among the five patients who died due to thromboembolic pulmonary hypertension with or without an acute PE, four were men, and the average number of days between the index event and death was 741 days ± 530 (range 286–1,652).

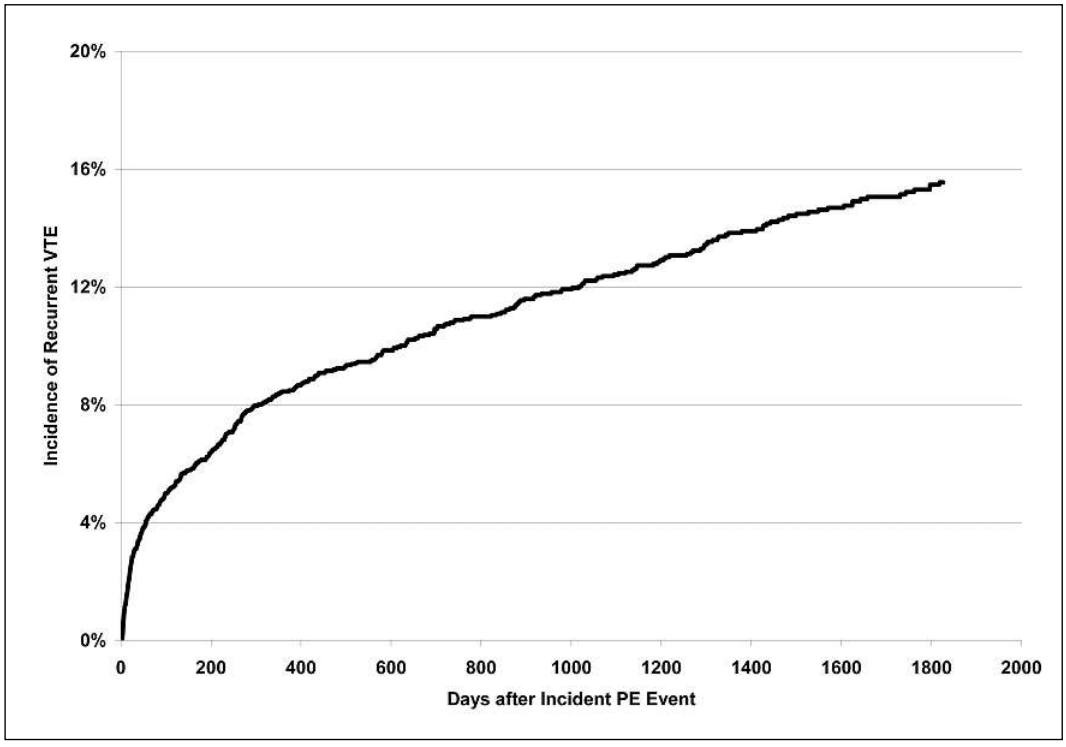


**Figure 2: Kaplan-Meier plot of incidence of recurrent PE (recurrent PE) after first-time idiopathic PE.**

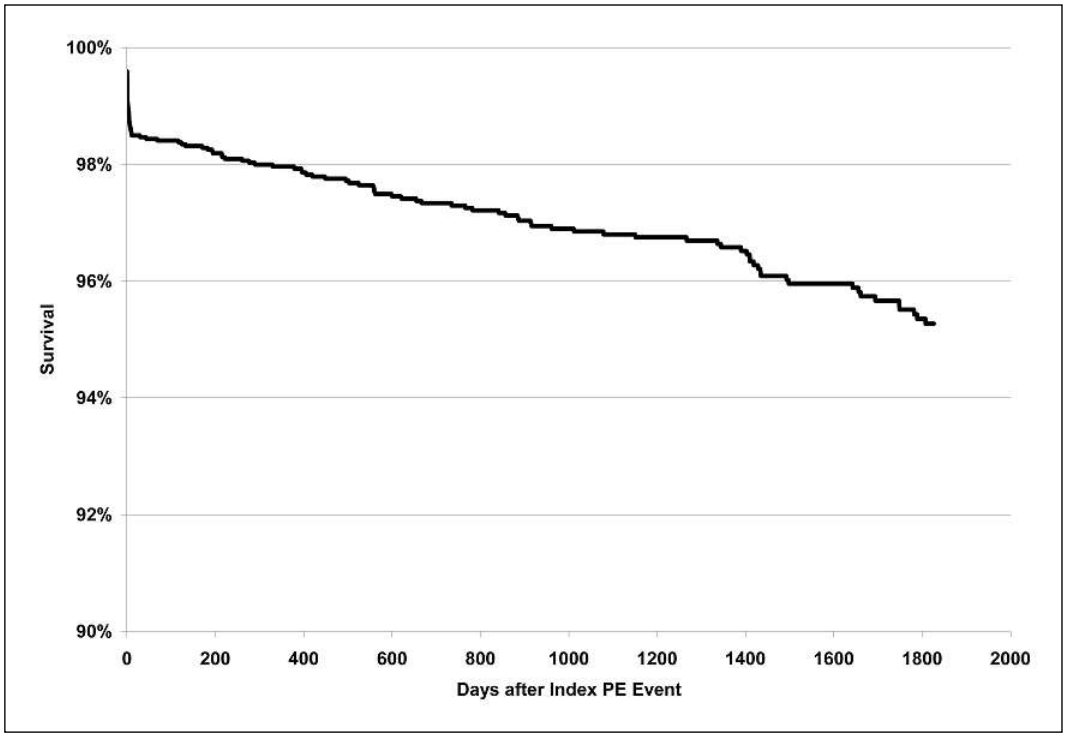


**Figure 3: Kaplan Meier plot of survival after incident idiopathic PE.**

The person-time rate of death (deaths per 100 patient-years) due to recurrent PE between three to six months, seven to 12 months, 13 to 24 months, and 25 to 60 months after the index PE event was 0.13% (CI=0.06–0.6%), 0.13% (CI=0.02–0.43%), 0.19% (CI=0.07–0.42%), and 0.17% (CI=0.08–0.32%), respectively. The annualized rate (= events/100 patients/year) of death due to PE in months 0–6 months after the index event was 3.2% per year (CI=2.4%-4.2%) whereas from six months to five years the rate was 0.16% (CI=0.1–0.26%) per year.

Among the 48 later deaths more than 29 days after the index PE that were adjudicated to be unrelated to VTE, the cause of death listed on the death certificate was major bleeding in three

cases, cardiac disease in seven, cancer in seven, HIV in six, infection or sepsis in four, sickle cell disease in three, chronic neurological disease in four, stroke in two, chronic lung disease in two, and other conditions in 10, including systemic lupus, chronic kidney disease, hepatitis C and suicide. Ten of these cases had undergone autopsy. In the majority of these cases, the cause of death on the death certificate was listed as a concurrent medical condition during either the index hospitalization for PE or one of the intervening hospitalizations, indicating a high degree of diagnostic consistency. In eight cases, however, the death certificate listed a diagnosis that was not listed as an active medical problem during any prior hospitalization. However, all eight of these cases died more than 550 days after the index event (range=1.5–4.8 years), and seven of them had no hospitalization record within a year prior to death. However, six of the eight had undergone an autopsy, lending credence to the death certificate diagnosis .

### Death in relationship to recurrent VTE

Of the 448 cases with recurrent VTE, 23 (5.2%) died during the follow-up period, and 12 of these cases died within 28 days of the recurrent event (case-fatality rate = 2.7%, 95%CI = 1.4–4.6%).

### Bleeding

During the average 3.2 years of follow-up, 280 (8.1%) cases were hospitalized with a principal diagnosis of bleeding. The rate of hospitalization for bleeding was 13.4 bleeds per 100 person-years in the first six months after the index event, 8.4 bleeds per 100 person-years in the next six months ($p<0.001$), 7.1 bleeds per 100 person-years one to two years after the index VTE ($p=0.17$ vs. 6 months to 1 year) and 5.7 bleeds per 100 person-years 2–5 years after the index event ($p=0.02$ vs. 1–2 years). Three cases died of bleeding more than 28 days after the index hospitalization for PE, one with an intra-cerebral bleed and one with a death certificate diagnosis of a 'coagulation defect' that underwent autopsy, and another case of intracranial bleeding.

## Discussion

The aim of this retrospective observational study was to estimate the incidence of death due to recurrent PE between six months and five years following diagnosis of acute idiopathic PE in a cohort of younger healthier patients. Because there was no specific information available regarding the duration or intensity of oral anticoagulant therapy in these patients, inferences regarding the inherent risk of fatal recurrent PE off anticoagulation therapy can not be made, and this will require prospective clinical trials. Nevertheless, the findings of this study are valuable because the cohort studied was population-based, racially/ethnically heterogeneous and the outcome of death could be readily ascertained. The findings reflect the "real world" incidence of death following a first-time diagnosis of unprovoked PE in patient treated in the community. The results of this study when coupled with the findings of prospective clinical trials, provide important information that help inform clinicians about the long-term risk of death due to recurrent PE in similar patients.

The major finding of this study was that the overall incidence of death during or following the index hospitalization for idiopathic PE was low, and the incidence of death due to recurrent thromboembolic disease was quite rare. Only 118 (3.5%) patients in this younger, healthier cohort died during the average follow-up period of 3.2 years, and close to half of these deaths (44%) occurred during the index hospital stay. Nevertheless, there were 66 late deaths that occurred more than 28 days after the initial index PE event and 18 (27% of late deaths, 0.5% of the entire cohort) of these were judged to have likely died as a consequence of either an acute recurrent PE (n=13) or PE coupled with development of pulmonary hypertension (n=5). Only 10 of the thromboembolic deaths (0.3% of the total cohort) were judged to be a result of a first-time recurrent VTE event. The remaining eight cases had one or more hospitalization for recurrent VTE between the index PE hospitalization and the event that led to death. Overall, the annualized rate of death that could be attributed to recurrent thromboembolic disease was very constant, ranging between 0.13%- 0.19% starting three months after the index PE event and going out to five years after the index event. This rate was slightly lower than the rate of fatal recurrent PE that was recently estimated by Douketis et al., 0.2%-0.5% per year, who studied an older cohort of patients (16).

Another important findings was that 68% of all of the patients who were hospitalized for recurrent VTE events were diagnosed as having a PE, which is consistent with the observation that patients who present with an index PE event are much more likely to be develop recurrent PE compared to a DVT (28). A third important finding was that in this younger healthier cohort, the 28-day case-fatality rate for first-time recurrent VTE was quite low, only 2.7%.

A noteworthy finding was that five of the 18 patients that died of recurrent thromboembolism were classified as having chronic pulmonary hypertension, as each had at least one hospitalization for recurrent PE event and were subsequently diagnosed with pulmonary hypertension (29). None of these patients had a diagnosis of pulmonary hypertension before or at the time of the index PE event. Interestingly, four of the five were men and the deaths occurred an average of approximately two years after the index event. It is possible that some of the cases that died suddenly out of the hospital had pulmonary hypertension, although this was not listed as the cause of death on their death certificate. These findings suggests that patients with chronic thromboembolic pulmonary hypertension make up an appreciable percentage of the deaths caused by thromboembolic disease, and that most of these patients have one or more hospitalization for recurrent PE before the pulmonary hypertension becomes clinically evident. In a recent study by Pengo et al. (30), the incidence of chronic thromboembolic pulmonary hypertension (CTPH) within two years after an index PE was 4%. Future prospective studies are needed to determine how frequently pulmonary hypertension develops after a single episode of PE versus multiple episodes of PE.

In this large population-based study, the 28-day case-fatality rate after a first-time PE was 1.5% and the six-month case-fatality rate was 1.7%. This is significantly lower than the early death rate of 8.1% recently reported in a much smaller and older cohort of patients diagnosed with acute PE (30). However, the case-fatality rate that we observed was close to the three-month case fatality rate of 2.3% that was reported in a large meta-analysis of

patients being treated for PE by Douketis et al. (8). The low case-fatality rate that we observed in the present study likely reflects the lower lethality of recurrent PE in patients under the age of 55 who have at most one chronic medical co-morbidity.

There were several important limitations to this study. First, we were able to analyze only patients who survived sufficiently long to be admitted to an acute care hospital and be diagnosed with acute PE. Second, it is likely that a modest percentage of the cases did not have objectively confirmed PE because of the inherent inaccuracy of the diagnostic tests (lung scanning and first generation computed tomography [CT] scanning) that were used during the time period studied, 1994–2001 (31, 32). However, one careful retrospective study from the early 1990s found little evidence of over diagnosis of PE (33). Nevertheless, to the degree that PE was over-diagnosed, the risk of death due to recurrent PE would have been underestimated. Third, we did not have any information about the presence or absence of a thrombophilic disorder.

Another limitation of this study was the absence of any information about long-term use of oral anticoagulants. During the time of this study, from 1994 through 2001, long-term use of oral anticoagulation after an initial episode of VTE was not standard in the United States or any other country. An estimate of the percentage of patients treated for VTE for longer than six months was recently provided by Prandoni et al. in a study from Italy. Among 1,600 patients without cancer who were treated for a first-time VTE event between 1991 and 2003, only 17% of the cases were treated with oral anticoagulation for over six months, and less than 5% were treated for over a year (34). If one assumes that 20% of the patients in the current study were maintained on chronic oral anticoagulation indefinitely and that that chronic anticoagulation treatment was 90% effective in preventing recurrent VTE (35, 36), the results of the current study may have underestimated the true rate of recurrent VTE and death six months to five years after the index VTE event by approximately 20%. Thus, the estimated annual rate of death from recurrent thromboembolism may be closer to between 0.20 to 0.35 deaths per 100 patients per year.

Although an effort was made to select only younger, healthier patients with PE, approximately 40% had at least one chronic medical co-morbid condition listed in their hospital records and many patients had a significant underlying medical disease, such as lupus erythematosus, chronic cardiomyopathy, amyotrophic lateral sclerosis or sickle cell disease. In fact at the time of death, only eight of the 18 patients whose death was attributed to recurrent VTE had no evidence of a significant medical co-morbid illness. Five had an underlying chronic illness and five had pulmonary hypertension. Further research is needed to determine to what degree underlying chronic co-morbidity contributes to the risk of recurrent VTE, particularly fatal PE.

Although the yearly incidence rate of fatal recurrent PE was very low, the observed incidence of death due to fatal bleeding even lower, as only one patient died of hemorrhage in the first six months after the index event, and only three additional patients died of bleeding beyond six months. However, lacking data about the use or non-use of anticoagulation therapy it is impossible to estimate the relative risk of death due to bleeding versus the death due to recurrent thrombosis.

In conclusion, in this population-based analysis of younger healthier patients diagnosed with acute idiopathic PE, the incidence of death due to first-time recurrent thromboembolism between one month and five years following diagnosis was very low, occurring in only 10 of 3,456 patients (0.3%). Overall, only 18 (0.5%) patients that died more than 28 days after their index hospitalisation died of recurrent thromboembolism during the follow up period that averaged 3.2 years. Among the patients that died of recurrent thromboembolism, death was attributed to thromboembolic pulmonary hypertension with or without acute recurrent PE in 28%. This rather high proportion of deaths due to pulmonary hypertension supports the recommendation (29, 30) that patients with PE should undergo a standardized evaluation at the end of the period of anticoagulation treatment to determine the presence or absence of chronic unresolved PE leading to pulmonary hypertension.

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