

Predictors of Survival After Deep Vein Thrombosis and Pulmonary Embolism

A Population-Based, Cohort Study

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Background: Because reported survival after venous thromboembolism (VTE) varies widely, we performed a population-based retrospective cohort study to estimate survival, compare observed with expected survival, and determine predictors of short-term (≤ 7 days) and long-term survival (> 7 days) after VTE.

Methods: We followed the 25-year (1966-1990) inception cohort ($n = 2218$) of Olmsted County, Minnesota, patients with deep vein thrombosis alone (DVT) or pulmonary embolism with or without deep vein thrombosis (PE \pm DVT) forward in time until death or the last clinical contact.

Results: During 14 629 person-years of follow-up, 1333 patients died. Seven-day, 30-day, and 1-year VTE survival rates were 74.8% (DVT, 96.2%; PE \pm DVT, 59.1%), 72.0% (DVT, 94.5%; PE \pm DVT, 55.6%), and 63.6% (DVT, 85.4%; PE \pm DVT, 47.7%), respectively. Observed survival after DVT, PE \pm DVT, and overall was significantly worse than expected for Minnesota whites of similar age and sex ($P < .001$). More than one third of deaths occurred on the date of onset or

after VTE that was unrecognized during life. Short-term survival improved during the 25-year study period, while long-term survival was unchanged. After adjusting for comorbid conditions, PE \pm DVT was an independent predictor of reduced survival for up to 3 months after onset compared with DVT alone. Other independent predictors of both short- and long-term survival included age, body mass index, patient location at onset, malignancy, congestive heart failure, neurologic disease, chronic lung disease, recent surgery, and hormone therapy. Additional independent predictors of long-term survival included tobacco smoking, other cardiac disease, and chronic renal disease.

Conclusions: Survival after VTE, and especially after PE \pm DVT, is much worse than reported, and significantly less than expected survival. Compared with DVT alone, symptomatic PE \pm DVT is an independent predictor of reduced survival for up to 3 months after onset, implying that treatment for the 2 disorders should be different.

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PULMONARY EMBOLISM is regarded as an uncommon cause of death when clinically recognized and appropriately treated.¹⁻⁶ Indeed, in the absence of recurrent embolism, death usually is attributed to comorbid disease rather than to the pulmonary embolism itself. Consequently, prevailing medical care with either standard anticoagulation therapy or an inferior vena cava filter primarily provides prophylaxis against recurrent pulmonary embolism from the presumed source, deep vein thrombosis of the leg or pelvis.^{3,5,7}

However, reported survival after venous thromboembolism varies widely, with "short-term" survival ranging from 95% to 97% for deep vein thrombosis^{8,9} and from 77% to 94% for pulmonary embolism,^{4,6,8,9} while "long-term" survival ranges from 61% to 75% for both deep vein thrombosis and pulmonary embolism.^{6,8-11}

This wide variability is likely due to limitations in study design. For example, studies that identified cases from acute care hospital discharge data¹²⁻¹⁴ or Medicare claims diagnoses^{8,15} are limited by diagnostic uncertainty or misclassification, as well as failure to include autopsy-discovered cases or to accurately separate initial from recurrent events. Such studies also may have missed venous thromboembolism patients dying in nursing homes or other chronic care facilities or rapidly fatal cases within the community.^{9,10} Other studies reporting data from selected populations, such as patients 65 years or older,^{8,15} patients referred to tertiary care centers,^{3,11} or patients enrolled in clinical trials,^{1,2,4,6} may not estimate true survival accurately since the full spectrum of disease is not represented. Moreover, use of the in-hospital pulmonary embolism case-fatality rate as a surrogate

METHODS

STUDY SETTING AND DESIGN

Using the data resources of the Rochester Epidemiology Project,¹⁶ we identified the inception cohort of Olmsted County, Minnesota, residents with a first lifetime deep vein thrombosis or pulmonary embolism during the 25-year period, 1966 through 1990. A master list of residents with deep vein thrombosis, pulmonary embolism, or similar diagnoses, or who had any diagnostic test or procedure that could be used in the diagnosis of deep vein thrombosis or pulmonary embolism was constructed by searching all available computer databases, logbooks, and other records of local health care providers. All subjects were followed forward in time through their linked medical records in the community (retrospective cohort study) until death, the most recent clinical contact, or July 19, 1994. For each subject, all inpatient and outpatient medical records of any local health care provider were searched for vital status at last clinical contact. For deceased patients, all death certificates were reviewed regardless of location at death. The study protocol was reviewed and approved by the Mayo Clinic Institutional Review Board.

DEFINITION OF DEEP VEIN THROMBOSIS AND PULMONARY EMBOLISM

Each episode of deep vein thrombosis or pulmonary embolism was categorized into the highest possible of 3 levels of diagnostic certainty ("definite," "probable," or "possible") according to previously defined criteria.¹⁷ A deep vein thrombosis was categorized as "definite" when confirmed by venography, computed tomographic scan, magnetic resonance imaging, or pathologic examination of thrombus removed at surgery or autopsy; as "probable" if testing for the definite level of diagnostic certainty was either not performed or indeterminate and at least one of the following noninvasive tests was positive: impedance plethysmography, continuous wave Doppler ultrasound examination performed in the Mayo Clinic Vascular Laboratory, compression duplex ultrasonography, radionuclide venography, or radiolabeled fibrinogen leg scan; and as "possible" if confirmatory tests were not done or were indeterminate and (1) the medical record indicated that a physician made a diagnosis of deep vein thrombosis (or possible deep vein thrombosis), (2) signs and symptoms consistent with deep vein thrombosis were present, and (3) the patient received a course of anticoagulation therapy with heparin, warfarin, or a similar agent or a surgical procedure for deep vein thrombosis. A pulmonary embolism was categorized as "definite" when confirmed by pulmonary angiography, computed tomographic scan, magnetic resonance imaging, or pathologic examination of thrombus removed at surgery or autopsy; as "probable" if testing for the definite level of diagnostic certainty was either not per-

formed or indeterminate and a perfusion or ventilation-perfusion lung scan was interpreted as high probability for pulmonary embolism; and as "possible" if confirmatory tests were either not done or were indeterminate and (1) the medical record indicated that a physician made a diagnosis of pulmonary embolism, (2) signs and symptoms consistent with pulmonary embolism were present, and (3) the patient received a course of anticoagulation therapy with heparin, warfarin, or a similar agent or a surgical procedure for pulmonary embolism such as an inferior vena cava filter. A short period of anticoagulation therapy while awaiting completion of diagnostic evaluation for either suspected deep vein thrombosis or pulmonary embolism was insufficient grounds for inclusion. An episode of venous thromboembolism consisting of both deep vein thrombosis and pulmonary embolism was categorized into the highest level of diagnostic certainty present for either manifestation. Because pulmonary embolism is a complication of deep vein thrombosis, results are presented as deep vein thrombosis alone or pulmonary embolism with or without deep vein thrombosis. During the course of the study, routine diagnostic testing for acute pulmonary embolism among patients with deep vein thrombosis was not performed unless there was additional clinical evidence of pulmonary embolism.

Venous thromboembolism events first identified during the patient's lifetime and meeting our diagnostic criteria, as well as autopsy-confirmed events, which had been objectively verified by an invasive or noninvasive test on the date of death, were classified as "antemortem-discovered." Autopsy-confirmed events meeting only our diagnostic criteria for a possible deep vein thrombosis or pulmonary embolism on the date of death, or autopsy-discovered events for which medical record review could not establish the date of onset, were classified as "postmortem-discovered" events. During the course of the study,¹⁸ the Olmsted County autopsy rate decreased from approximately 60% during the early study years to approximately 35% during the later years (P. N. Nemetz, MD, unpublished data, 1997).

Mayo Clinic pathologists performed all autopsy examinations and completed the death certificates of persons dying within Olmsted County during the study period. Postmortem-discovered pulmonary embolism events were classified as a "cause of death" only if the pathologist labeled it as such in the autopsy report, or if the death certificate listed pulmonary embolism as an immediate or underlying cause of death, or included pulmonary embolism on part 1 of the death certificate. Postmortem-discovered pulmonary embolism events were classified as a "contributory cause of death" if pulmonary embolism was listed as a contributing cause or other significant condition on part 2 of the death certificate. Pulmonary embolism events first identified on postmortem examination but not specifically labeled as a "cause of death" in the autopsy report or listed on the death certificate were categorized as

measure for short-term survival^{9,12-14} may be misleading as case-fatality rates are not a life-table analysis. Information regarding long-term survival is limited since the duration of follow-up in most studies is only 1 to 3 years,^{4,9} with only 2 studies reporting follow-up to 8 years.^{10,11} Two studies have compared survival after pulmonary embolism with expected survival,^{6,8} but both were restricted to special populations. Consequently, the difference between observed survival after deep vein thrombosis or pulmonary embolism and expected survival is uncertain. Finally, 2 studies have reported independent predictors of survival after venous thromboembolism, but

“noncausal for death.” Patients were excluded who otherwise met our criteria for possible deep vein thrombosis or pulmonary embolism and who died within 7 days of onset but deep vein thrombosis or pulmonary embolism could not be confirmed at autopsy.

POTENTIAL PREDICTORS OF SURVIVAL

A large number of baseline characteristics were tested as predictors of survival after the initial episode of venous thromboembolism. Data on these characteristics were collected by review of all medical records (inpatient and outpatient) in the community for each subject. The characteristics included the following: type of event (pulmonary embolism, deep vein thrombosis, or both); age, sex, and year of incident event; patient location at onset (community, hospital, or nursing home); body mass index (BMI) (calculated as weight in kilograms divided by the square of height in meters) categorized as “underweight” ($BMI < 20$), “normal weight” ($20 \leq BMI \leq 24$), “overweight” ($24 < BMI < 30$), or “obese” ($BMI \geq 30$); chronic heart disease (congestive heart failure, other heart disease [congenital heart disease, cardiomyopathy, ischemic heart disease, or valvular heart disease]); active malignancy (excluding nonmelanoma skin cancer), with or without chemotherapy (cytotoxic or immunosuppressive therapy for malignancy, excluding tamoxifen); serious neurologic disease (stroke or other disease affecting the nervous system with associated extremity paresis, or acute stroke with extremity paresis requiring hospitalization within the previous 3 months); surgery requiring anesthesia (general, orthopedic, neurologic, or gynecologic surgery); anesthesia (general, epidural/spinal, other); trauma requiring hospital admission (major fracture or severe soft tissue injury); chronic lung disease (chronic obstructive pulmonary disease, emphysema, chronic bronchitis, bronchiectasis, interstitial lung disease, pulmonary hypertension; asthma included only if documented evidence of fixed airflow obstruction); chronic liver disease (including active hepatitis within the previous 3 months); chronic renal disease (physician’s diagnosis and creatinine levels of $>176.8 \mu\text{mol/L}$ [$>2 \text{ mg/dL}$] for at least 3 months, or nephrotic syndrome); hormone therapy (estrogen or progesterone); myeloproliferative disease; inflammatory bowel disease; smoking status (none, former, or current; considering cigarettes only); and for women only: pregnancy or postpartum at the time of the incident event; oral contraceptive therapy; or tamoxifen therapy. Active malignancy, chemotherapy, all surgery variables, anesthesia, trauma, hormone therapy, oral contraceptive therapy, and tamoxifen therapy were recorded as present only if documented within the 3 months prior to the venous thromboembolic event. Congestive heart failure, serious neurologic disease, chronic lung disease, chronic liver disease, chronic renal disease, myeloproliferative diseases, and inflammatory bowel disease were recorded as present if documented any time prior to the in-

cident venous thromboembolic event. Body mass index calculations were based on the most recent height and weight measurements prior to the incident event. Body mass index could not be calculated in 82 cases because of missing weight or height (or both). For these cases, BMI values were imputed by assigning to each case the average height and/or weight of those incident cases of the same sex and age group. Smoking status was based on tobacco use in the 3 months prior to the incident event.

DATA ANALYSIS

Due to the relatively high autopsy rate during the study period, a substantial number of incident cases of venous thromboembolism were first identified at autopsy and the time interval from onset to death could not be determined. For purposes of analysis, these cases were grouped with those whose death was known to have occurred within 7 days of the diagnosis of venous thromboembolism. Consequently, most of the venous thromboembolism cases categorized as dying within 7 days of onset were postmortem-discovered events. Therefore, we performed 2 analyses: an analysis of those who died within 7 days of the incident event (including postmortem-discovered events) (short-term survival) and an analysis of those who survived at least 7 days after the incident event (long-term survival).

Evaluation of baseline characteristics as predictors of short- or long-term survival was performed using logistic regression models (no subjects were lost to follow-up within the first 7 days) and Cox proportional hazards models, respectively. In each instance, stepwise forward and backward modeling were performed to screen potential variables for inclusion in the final model, with a P value of $\leq .10$ required for a variable to enter and/or leave each model. The selection of variables to be included in all final models was validated using bootstrap methods.¹⁹ This involves selecting, with replacement from the appropriate study cohort, at least 500 samples of the same size as the cohort and determining which variables would be included in the model from each of the 500 samples. Only if a variable was included in at least 70% of models was it considered for inclusion in our final model. For the Cox model, the proportional hazards assumption was assessed for all variables. When the proportional hazards assumption failed, lack of proportionality was accounted for in the modeling. For the calculation of expected survival, the Minnesota white population was used to develop a hypothetical cohort of individuals of identical age, sex, and follow-up period as our study group.²⁰

Because of incomplete information regarding smoking status, the smoking variable was assessed as a potential predictor of survival only after determining the otherwise final model. Similarly, because pregnancy, postpartum state, oral contraceptive use, and tamoxifen therapy pertained only to women, these variables also were assessed only after determining the otherwise final model.

both were limited in the number of covariates that could be tested because of sample size constraints.^{4,10}

To address these limitations, we identified the inception cohort of Olmsted County, Minnesota, residents with deep vein thrombosis or pulmonary embolism first diagnosed during the 25-year period, 1966

through 1990, and performed a population-based follow-up study to estimate short-term and long-term survival, to compare observed survival with age- and sex-adjusted expected survival, and to determine independent predictors of short-term and long-term survival after incident venous thromboembolism.

Table 1. Kaplan-Meier Estimates of Survival After Deep Vein Thrombosis (DVT) Alone, Pulmonary Embolism (PE) With or Without DVT (PE ± DVT), and All Venous Thromboembolism (VTE) Among Olmsted County, Minnesota, Residents With First Lifetime VTE Diagnosed, 1966-1990

Time	PE ± DVT, %			All VTE§
	DVT Alone*	All PE†	PE as Cause of Death‡	
0 d	97.0	63.6	76.5	77.7
7 d	96.2	59.1	71.1	74.8
14 d	95.7	57.1	68.7	73.3
30 d	94.5	55.6	66.8	72.0
90 d	91.9	52.1	62.8	68.9
1 y	85.4	47.7	57.4	63.6
2 y	81.4	44.6	53.6	60.1
5 y	72.6	39.4	47.4	53.5
8 y	65.2	34.5	41.5	47.5

*All 938 DVT cases, including 28 autopsy-discovered DVT cases (eg, 0 days = 28/938).

†All 1280 PE cases, including 461 autopsy-discovered PE cases and 5 antemortem-diagnosed PE cases (eg, 0 days = 466/1280).

‡Excludes 216 cases in which autopsy-discovered PE was categorized as "noncausal for death."

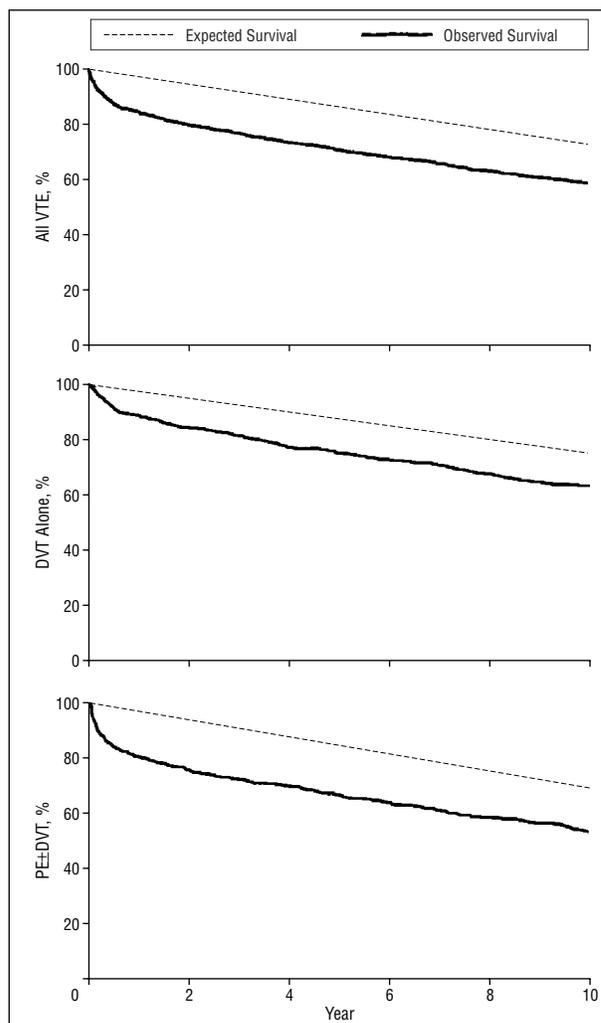
§Includes all 2218 cases, including 489 autopsy-discovered VTE cases and 5 antemortem-diagnosed PE cases (eg, 0 days = 494/2218).

RESULTS

After screening 9046 potential cases, 2218 Olmsted County residents were identified who had a confirmed first lifetime diagnosis of deep vein thrombosis or pulmonary embolism between January 1, 1966, and December 31, 1990. The mean age at onset was 61.7 ± 20.4 years (mean \pm SD) and 1244 (56%) patients were female. Nine hundred thirty-eight (42%) patients had deep vein thrombosis, while 969 (44%) had pulmonary embolism and 308 (14%) had evidence of both deep vein thrombosis and pulmonary embolism; 3 (0.1%) patients had chronic thromboembolic pulmonary hypertension.

SURVIVAL AFTER VENOUS THROMBOEMBOLISM

The 2218 patients were followed up for a total of 14 629 person-years after the event date (6.6 ± 7.3 years; median, 4.0 years), during which 1333 patients died. The median duration of follow-up was 7.2 years for patients with deep vein thrombosis and 0.4 years for those with pulmonary embolism. However, 494 (37.1%) of the 1333 patients died on the day of onset or were dead at discovery of venous thromboembolism, including 489 (36.7%) patients (28 deep vein thrombosis alone, 461 pulmonary embolism with or without deep vein thrombosis) whose event date was either the same as the date of death or who had postmortem-discovered venous thromboembolism. After excluding autopsy-discovered cases, the median duration of follow-up was 7.4 years for deep vein thrombosis and 6.1 years for pulmonary embolism. Of the 461 patients with postmortem-discovered pulmonary embolism, 245 (53%) were classified by a patholo-



Observed survival after all venous thromboembolism (VTE), deep vein thrombosis (DVT) alone, and pulmonary embolism (PE) with or without deep vein thrombosis (PE ± DVT), conditional on surviving for 7 days, among Olmsted County, Minnesota, residents with a first lifetime VTE during the study period, 1966-1990, compared with expected survival based on Minnesota whites of like age and sex.

gist as an "immediate," "underlying," or "contributory" cause of death.

The overall 1-day survival after venous thromboembolism was 77.7%, but 1-day survival for patients with deep vein thrombosis alone was 97.0% compared with 63.6% for those with pulmonary embolism (Table 1). Overall 7-day survival was 74.8%; however, 96.2% of those with deep vein thrombosis were still alive at 7 days compared with only 59.1% of those with pulmonary embolism. If those postmortem-discovered pulmonary embolism events that were categorized as not causal for death are excluded, 71.1% of patients with pulmonary embolism survived 7 days. The Kaplan-Meier estimated probabilities of survival at later dates after onset of venous thromboembolism are shown in Table 1.

Even for the 1660 patients who were still alive 7 days after diagnosis, subsequent survival was significantly worse than that expected ($P < .001$, Figure). This was true for patients with deep vein thrombosis alone as well as for

Table 2. Univariate Logistic Analyses of Potential Predictors of Death Within 7 Days After Venous Thromboembolism Among Olmsted County, Minnesota, Residents With First Lifetime Venous Thromboembolism Diagnosed, 1966-1990*

Characteristic	Odds Ratio	95% CI
Demographic Characteristics and Health Habits		
Age, per decade	1.61	1.51-1.72
Male sex	1.10	0.91-1.34
Event year (per increasing year)	0.97	0.96-0.98
Weight, per 10 kg	0.67	0.63-0.71
Body mass index (BMI), kg/m ²		
Underweight (BMI <20)	3.48	2.66-4.54
Normal weight (20 ≤ BMI ≤ 24)	1.00	...
Overweight (24 < BMI < 30)	0.52	0.40-0.67
Obese (BMI ≥ 30)	0.33	0.22-0.47
Smoking status		
Never	1.00	...
Current	0.63	0.48-0.83
Former	1.11	0.87-1.41
Location at venous thromboembolism onset		
Community	1.00	...
Hospital	7.79	6.11-9.94
Nursing home	12.49	9.08-17.18
Medical Diagnoses		
Congestive heart failure†	4.63	3.67-5.84
Neurologic disease†	3.61	2.68-4.86
Chronic lung disease†	2.67	2.07-3.43
Chronic renal disease†	2.40	1.36-4.22
Chronic liver disease†	1.72	0.84-3.51
Myeloproliferative disorder†	3.35	1.35-8.29
Trauma†	0.86	0.66-1.13
Malignancy		
None	1.00	...
Malignancy without chemotherapy	3.53	2.70-4.61
Malignancy with chemotherapy	2.87	1.19-4.31
Surgery/Anesthesia/Therapy		
General surgery†	1.14	0.86-1.52
Orthopedic surgery†	0.55	0.38-0.80
Neurosurgery†	0.84	0.43-1.65
Anesthesia type		
None	1.00	...
General	0.64	0.51-0.81
Epidural/spinal	0.69	0.33-1.46
Other	0.10	0.01-0.74
Any surgery and the interval between surgery and venous thromboembolism		
No surgery in previous 90 d	1.00	...
Surgery within previous 0-21 d	0.58	0.44-0.76
Surgery within previous 22-90 d	1.04	0.73-1.49
Hormone therapy†	0.39	0.22-0.69
Gynecologic Characteristics‡		
Gynecologic surgery†	0.24	0.10-0.61
Postpartum†	0.05	0.01-0.36
Oral contraceptive therapy†	0.08	0.03-0.26
Tamoxifen†	2.25	0.71-7.13

*CI indicates confidence interval. Ellipses indicate data not applicable.

†The comparison group lacks the indicated characteristic.

‡There were no deaths among those women whose venous thromboembolism was diagnosed during pregnancy.

patients with pulmonary embolism with or without deep vein thrombosis. For patients who survived for a full year after venous thromboembolism, subsequent survival was still worse than expected, overall (at 8 years, 71.6% vs 80.3%) as well as after deep vein thrombosis alone (at 8

Table 3. Multivariate Logistic Analysis of Potential Predictors of Death Within 7 Days After Venous Thromboembolism Among Olmsted County, Minnesota, Residents With First Lifetime Venous Thromboembolism Diagnosed, 1966-1990

Characteristic	Odds Ratio	95% CI
Event year (per increasing year)	0.96	0.94-0.98
Male sex (among patients with no malignancy)	1.44	1.07-1.93
Body mass index (BMI), kg/m ²		
Underweight (BMI <20)	2.67	1.92-3.71
Normal weight (20 ≤ BMI ≤ 24)	1.00	...
Overweight (24 < BMI < 30)	0.63	0.46-0.86
Obese (BMI ≥ 30)	0.56	0.36-0.86
Location at onset of venous thromboembolism and patient's age, y		
Community		
45	1.00	...
60	2.05	1.63-2.57
75	4.18	2.65-6.60
Hospital		
45	13.68	8.07-23.17
60	17.92	11.00-29.19
75	23.48	14.33-38.48
Nursing home		
45	8.64	2.96-25.19
60	12.32	5.77-26.29
75	17.57	10.02-30.81
Neurologic disease†	1.68	1.16-2.44
Chronic lung disease†	1.41	1.01-1.95
Congestive heart failure†	2.31	1.72-3.11
Malignancy without chemotherapy‡		
Female	7.04	4.26-11.63
Male	2.38	1.47-3.86
Malignancy with chemotherapy‡		
Female	4.13	2.02-8.45
Male	8.52	3.76-19.27
Any surgery and the interval between surgery and venous thromboembolism		
No surgery in previous 90 d	1.00	...
Surgery within previous 0-21 d	0.36	0.25-0.51
Surgery within previous 22-90 d	0.71	0.45-1.12
Hormone therapy†	0.34	0.17-0.71

*CI indicates confidence interval. Ellipses indicate data not applicable.

†The comparison group lacks the indicated characteristic.

‡Compared with female patients with no malignancy.

years, 73.0% vs 81.7%) and after pulmonary embolism with or without deep vein thrombosis (at 8 years, 69.7% vs 78.5%; all 1-sample log-rank $P < .001$).

PREDICTORS OF SHORT-TERM SURVIVAL

Five hundred fifty-eight patients were categorized as dying within 7 days of their incident venous thromboembolism event and none of the remaining 1660 patients were lost to follow-up within the first 7 days. The odds ratios (and associated 95% confidence intervals) for more than 25 baseline characteristics evaluated as potential predictors of 7-day survival are presented in **Table 2** (univariate analyses). Since 536 (96%) of the 558 patients dying within 7 days met our criteria for a definite event based on autopsy detection or confirmation, the level of diagnostic certainty (ie, definite, probable, or possible) was not assessed in the logistic model.

Table 4. Univariate Proportional Hazards Analyses of Potential Predictors of Time to Death, Conditional on Surviving 7 Days After Venous Thromboembolism Among Olmsted County, Minnesota, Residents With First Lifetime Venous Thromboembolism Diagnosed, 1966-1990*

Characteristic	Hazards Ratio	95% CI
Demographic Characteristics and Health Habits		
Age, per decade	1.91	1.81-2.01
Male sex	1.51	1.31-1.74
Event year (per increasing year)	1.03	1.02-1.04
Weight, per 10 kg	0.88	0.85-0.92
Body mass index (BMI), kg/m ²		
Underweight (BMI <20)	1.65	1.31-2.08
Normal weight (20 ≤ BMI ≤ 24)	1.00	...
Overweight (24 < BMI < 30)	0.82	0.69-0.97
Obese (BMI ≥ 30)	0.71	0.57-0.88
Smoking status		
Never	1.00	...
Current	0.72	0.59-0.87
Former	1.33	1.12-1.58
Location at venous thromboembolism onset		
Community	1.00	...
Hospital	1.55	1.32-1.82
Nursing home	4.04	3.21-5.08
Medical Diagnoses		
Heart disease		
None	1.00	...
Congestive heart failure	4.78	3.98-5.74
Other heart disease	2.64	2.18-3.19
Neurologic disease†	2.28	1.78-2.94
Chronic lung disease†	2.68	2.21-3.23
Chronic renal disease†	3.83	2.57-5.72
Chronic liver disease†	2.13	1.34-3.40
Myeloproliferative disorder†	2.58	1.22-5.42
Trauma†	0.97	0.78-1.21
Malignancy		
None	1.00	...
Malignancy without chemotherapy	4.51	3.67-5.53
Malignancy with chemotherapy	9.38	7.00-12.57

Although all autopsy-discovered cases of deep vein thrombosis were included, the type of venous thromboembolism event (deep vein thrombosis alone vs pulmonary embolism with or without deep vein thrombosis) was not assessed in the final modeling process because of potential bias favoring autopsy detection of pulmonary embolism over lower extremity deep vein thrombosis. However, since 40.9% of pulmonary embolism patients died within the first 7 days compared with only 3.7% of deep vein thrombosis patients (univariate odds ratio, 17.8), pulmonary embolism likely was a significant predictor of early death compared with deep vein thrombosis alone.

Many patient characteristics were interrelated as predictors of short-term survival, as shown in the multivariate logistic model (Table 3). Independent predictors of reduced short-term survival were increasing age, male sex, earlier event year, lower BMI, confinement to a hospital or nursing home at the onset of venous thromboembolism, and a history of congestive heart failure, chronic lung disease, neurologic disease, or malignancy. Short-term survival decreased with advancing age, but the rate of decrease varied by patient loca-

Table 4. Univariate Proportional Hazards Analyses of Potential Predictors of Time to Death, Conditional on Surviving 7 Days After Venous Thromboembolism Among Olmsted County, Minnesota, Residents With First Lifetime Venous Thromboembolism Diagnosed, 1966-1990* (cont)

Characteristic	Hazards Ratio	95% CI
Surgery/Anesthesia/Therapy		
General surgery†	1.05	0.85-1.30
Orthopedic surgery†	0.87	0.68-1.10
Neurosurgery†	0.96	0.57-1.60
Anesthesia type		
None	1.00	...
General	0.73	0.62-0.86
Epidural/spinal	0.82	0.46-1.45
Other	0.14	0.04-0.42
Any surgery and the interval between surgery and venous thromboembolism		
No surgery in previous 90 d	1.00	...
Surgery within previous 0-21 d	0.68	0.56-0.82
Surgery within previous 22-90 d	1.25	0.96-1.62
Hormone therapy†	0.73	0.53-1.00
Gynecologic Characteristics‡		
Gynecologic surgery†	0.32	0.17-0.60
Oral contraceptive therapy†	0.03	0.01-0.12
Tamoxifen†	4.86	2.16-10.95
Venous Thromboembolism		
Diagnostic certainty		
Possible	1.00	...
Definite/probable	1.22	1.05-1.41
Event type		
Deep vein thrombosis	1.00	...
Pulmonary embolism	1.45	1.26-1.67§

*CI indicates confidence interval. Ellipses indicate data not applicable.

†The comparison group lacks the indicated characteristic.

‡There were no deaths among those women whose venous thromboembolism was diagnosed either during pregnancy or post partum.

§P < .001, generalized log-rank test.²¹

tion at the onset of venous thromboembolism. Confinement to a hospital or nursing home at the time of venous thromboembolism onset was associated with worse survival over all ages. Among patients without malignancy, the odds of early death for males were 44% higher than for females. The odds of underweight patients (BMI < 20) dying within 7 days of venous thromboembolism were almost 3-fold higher than the odds for patients with normal weight (20 ≤ BMI ≤ 24), even after controlling for such potentially debilitating diseases as malignancy, congestive heart failure, chronic lung disease, and neurologic disease. Short-term survival also was decreased among venous thromboembolism patients with malignancy, but the rate of decrease varied by concurrent chemotherapy and sex. For example, among cancer patients who were not receiving chemotherapy, the odds of death within 7 days were almost 3-fold higher for females than males. Conversely, for cancer patients receiving chemotherapy, the odds of an early death were almost 2-fold higher for males than females.

Independent predictors of increased short-term survival after venous thromboembolism included higher BMI, hormone therapy, and recent surgery. Surprisingly, the

Table 5. Multivariate Proportional Hazards Analysis of Potential Predictors of Time to Death, Conditional on Surviving 7 Days After Venous Thromboembolism Among Olmsted County, Minnesota, Residents With First Lifetime Venous Thromboembolism Diagnosed, 1966-1990*

Characteristic	Hazards Ratio	95% CI
Male sex (among patients with no malignancy)	1.44	1.21-1.71
Body mass index (BMI), kg/m ²		
Underweight (BMI <20)	1.12	0.87-1.43
Normal weight (20 ≤ BMI ≤ 24)	1.00	...
Overweight (24 < BMI <30)	0.78	0.65-0.93
Obese (BMI ≥30)	0.70	0.56-0.87
Smoking status		
Never	1.00	...
Former smoker	1.22	1.01-1.48
Current smoker	1.60	1.29-1.97
Location at venous thromboembolism onset		
Community	1.00	...
Hospital	1.28	1.05-1.55
Nursing home	1.52	1.17-1.97
Neurologic disease†	1.75	1.33-2.30
Chronic lung disease†	1.35	1.10-1.66
Chronic renal disease†	3.46	2.28-5.24
Congestive heart failure and patient's age, y‡		
45	5.13	2.96-8.89
60	2.97	2.14-4.13
75	1.72	1.41-2.10
Other heart disease and patient's age, y‡		
45	1.67	1.04-2.70
60	1.45	1.10-1.91
75	1.26	1.03-1.55
Malignancy without chemotherapy§		
Age 45 y		
Female	22.12	12.85-38.09
Male	11.43	6.81-19.18
Age 60 y		
Female	12.64	8.56-18.66
Male	6.53	4.62-9.23
Age 75 y		
Female	7.22	5.03-10.37
Male	3.73	2.75-5.06
Malignancy with chemotherapy§		
Age 45 y		
Female	77.65	43.83-137.58
Male	85.73	49.74-147.78
Age 60 y		
Female	26.51	17.52-40.12
Male	29.27	17.94-47.77
Age 75 y		
Female	9.05	5.88-13.93
Male	9.99	5.52-18.10
Any surgery and the interval between surgery and venous thromboembolism		
No surgery in previous 90 d	1.00	...
Surgery within previous 0-21 d	0.61	0.49-0.77
Surgery within previous 22-90 d	0.67	0.51-0.87
Hormone therapy†	0.68	0.47-0.98

*CI indicates confidence interval. Ellipses indicate data not applicable.

†The comparison group lacks the indicated characteristic.

‡Compared at each age with patients with no congestive heart failure or other heart disease.

§Compared at each age with female patients with no malignancy.

odds of early death for venous thromboembolism patients who were overweight (24 < BMI < 30) or even obese (BMI ≥ 30) was significantly less than for the patients of

Table 6. Multivariate Proportional Hazards Analysis of Additional Risk of Death (Hazards Ratio) From Pulmonary Embolism With or Without Deep Vein Thrombosis Compared With Deep Vein Thrombosis Alone, Conditional on Surviving 7 Days After Venous Thromboembolism Among Olmsted County, Minnesota, Residents With First Lifetime Venous Thromboembolism, Diagnosed, 1966-1990*

Time Since Event, d	Days Since Event	No. of Cases at Risk	Hazard Ratio	95% CI
≤90	14	1635	5.68	2.28-14.19
	21	1618	3.66	1.96-6.84
	30	1598	2.72	1.75-4.23
	60	1552	1.67	1.26-2.20
	90	1523	1.29	0.92-1.80
>90	120	1492	1.27	0.93-1.72
	150	1472	1.25	0.94-1.66
	180	1446	1.24	0.95-1.61

*For hazard ratio, estimates adjusted for all the variables presented in Table 5. CI indicates confidence interval.

normal weight. The odds of early death were reduced by 65% among patients who developed venous thromboembolism while receiving hormone therapy compared with similar patients not receiving such therapy. Likewise, patients developing venous thromboembolism within 3 weeks after surgery had significantly better short-term survival than similar patients without recent surgery. Short-term survival among patients developing venous thromboembolism within 3 weeks to 3 months after surgery was no different compared with patients without recent surgery.

PREDICTORS OF LONG-TERM SURVIVAL

Of the 2218 incident venous thromboembolism patients, 1660 survived at least 7 days. The hazards ratios (and associated 95% confidence intervals) for baseline characteristics tested as predictors of long-term survival are presented in **Table 4** (univariate analyses). Again, many of these characteristics were interrelated as predictors of long-term survival, as shown in the final multivariate model (**Table 5** and **Table 6**). Independent predictors of reduced long-term survival included increasing age, event type, current or former tobacco smoking status, confinement to a hospital or nursing home at venous thromboembolism onset, and a history of congestive heart failure, chronic lung disease, chronic renal disease, neurologic disease, or malignancy. The level of diagnostic certainty (definite, probable, or possible) was not an independent predictor of long-term survival.

Even after controlling for comorbid diseases, long-term survival remained significantly reduced for patients with pulmonary embolism compared with patients with deep vein thrombosis alone (Table 6). However, this difference in survival decreased by time since the incident event; at 14 days following the incident event, pulmonary embolism patients had a 5.7-fold increased risk of death compared with patients with deep vein thrombosis alone. By 30 days, the excess risk of death for pulmonary embolism patients had fallen to

less than 3 times that of patients with deep vein thrombosis alone, and by 90 days the risk of death among patients with pulmonary embolism was not significantly different from patients with deep vein thrombosis alone.

Among patients without malignancy, male venous thromboembolism patients had a 44% increased risk of late death compared with similar female patients. The impact of age on long-term survival among venous thromboembolism patients without congestive heart failure, other cardiac disease, or malignancy was similar, with the risk of death increasing approximately 2-fold per decade of life. However, the impact of congestive heart failure on long-term survival after venous thromboembolism varied by age. Thus, 45-year-old, 60-year-old, and 75-year-old venous thromboembolism patients with congestive heart failure had approximately a 5-fold, 3-fold, and 1.7-fold increased risk of late death, respectively, compared with like-aged venous thromboembolism patients without congestive heart failure. In contrast, venous thromboembolism patients with other heart disease that was not complicated by congestive heart failure had only a modestly increased risk of late death over all ages.

The impact of malignancy on long-term survival after venous thromboembolism varied by concurrent chemotherapy, sex, and age. For example, female venous thromboembolism patients with malignancy and no concurrent chemotherapy had a 2-fold increased risk of late death over all ages when compared with similar male patients. In contrast, male venous thromboembolism patients with malignancy and concurrent chemotherapy had a slightly higher risk of late death compared with similar female patients, again over all ages. Reduction in long-term survival was most pronounced among younger venous thromboembolism patients with malignancy, regardless of sex or concurrent chemotherapy.

Independent predictors of increased long-term survival included higher BMI, hormone therapy, and recent surgery. Similar to the effect on short-term survival, overweight ($24 < \text{BMI} < 30$) and obese ($\text{BMI} \geq 30$) patients with venous thromboembolism had significantly better long-term survival compared with patients with normal body weight. Improved long-term survival also was observed in venous thromboembolism patients receiving hormone therapy, with a 30% reduction in the risk of late death compared with similar patients who were not receiving hormone therapy. Likewise, patients who had surgery within 90 days prior to the diagnosis of thromboembolism had significantly better long-term survival compared with similar patients without prior surgery.

COMMENT

We have determined survival in an inception cohort of patients from a well-defined geographic population,¹⁶ which included the full spectrum of disease in all clinical settings (the community, nursing home, and hospital) where venous thromboembolism may occur. In addition to our access to both outpatient and inpatient medical records, we used information from autopsy findings and death certificates to ensure essentially complete ascertainment of clinically recognized disease. As a consequence, the proportion of patients first discovered or confirmed at au-

topsy was greater than in most other series. For these 489 patients, the incident date of venous thromboembolism could not be precisely determined, precluding standard Kaplan-Meier analysis. However, even when the calculations were made conditional on living for at least 7 days, survival was still significantly worse compared with survival among Minnesota whites of similar age and sex. Observed survival was worse than expected for both deep vein thrombosis and pulmonary embolism patients, and remained so even for those patients surviving 1 year after venous thromboembolism.

Observed survival among patients in our cohort with symptomatic deep vein thrombosis and no clinically recognized pulmonary embolism was similar to previously reported rates.⁸⁻¹¹ However, survival among patients with pulmonary embolism was strikingly worse than previously reported.^{3,4,8,9} For example, our 1-week survival after pulmonary embolism (71.1%) was 25% lower than the reported 94.7% 1-week survival among patients enrolled in the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) clinical trial,^{4,22} even after we excluded autopsy-discovered pulmonary embolism classified as "noncausal for death." This discrepancy cannot be explained by differences in management since the vast majority (88%) of our patients whose conditions were diagnosed ante mortem received standard therapy. Instead, the difference is best explained by more complete case ascertainment in our study, as shown by the fact that exclusion of postmortem-discovered and immediately fatal events in our cohort produced a 1-week survival rate of 93% that is virtually identical to the PIOPED rate.⁴ Although the type of venous thromboembolism event (deep vein thrombosis alone vs pulmonary embolism with or without deep vein thrombosis) was not formally assessed in the logistic models for reasons of potential bias, the risk of early death among pulmonary embolism patients was nearly 18-fold higher than that of patients with deep vein thrombosis alone. Pulmonary embolism also was an independent predictor of late death. However, the excess risk of death after pulmonary embolism decreased with time, such that by 3 months following the incident event, the risk of death among pulmonary embolism patients was no different than among patients with deep vein thrombosis alone.

Calendar year also was an independent predictor of short-term survival, with a mean 4% per year improvement in short-term survival during the course of the 25-year study period. However, the vast majority (87.6%) of patients within our cohort who died within the first 7 days had their deep vein thrombosis or pulmonary embolism discovered at autopsy. Because the Olmsted County autopsy rate¹⁸ decreased from approximately 60% to 35% of deaths during the course of the study (P. N. Nemetz, MD, unpublished data, 1997), the observed improvement in short-term survival could have been confounded by the reduction in the autopsy rate. Although we cannot differentiate between these 2 possibilities, we believe any real improvement in short-term survival during the course of the study period likely was small and clinically unimportant. Previous studies reporting constant pulmonary embolism in-hospital case-fatality rates for the years 1979 to 1985 lend support to this interpre-

tation.^{13,14} Incidence year was a significant predictor of long-term survival in the univariate analysis but not in the multivariate model.

Additional independent predictors of reduced early and late survival after venous thromboembolism included congestive heart failure, chronic lung disease, and neurologic disease. Current or former cigarette smokers had significantly worse long-term survival, even after controlling for chronic cardiac and lung disease. Frailty, manifest as a below normal BMI or confinement to a hospital or nursing home, predicted lower survival after controlling for other debilitating comorbid illnesses. Conversely, survival was higher among patients likely to be in good health, such as overweight or obese patients, patients well enough to undergo surgery, or patients receiving hormone therapy. Malignancy was an independent predictor of reduced early and late survival after venous thromboembolism, but the influence of malignancy on short-term survival varied by sex and the administration of chemotherapy, while the influence of malignancy on long-term survival varied additionally by age.

In summary, overall survival after venous thromboembolism, and especially after pulmonary embolism, is much worse than previously reported and significantly less than expected survival. More than one third of the deaths occurred on the date of onset or followed venous thromboembolism unrecognized during life. For these patients, available time for diagnosis and treatment was insufficient to alter the natural history of their disease. After controlling for other comorbid diseases, pulmonary embolism remained a significant and independent predictor of survival for up to 3 months after onset. This is at variance with the conclusion that pulmonary embolism, when properly diagnosed and treated, is an uncommon primary cause of death.¹⁻⁶ In addition, we have shown that long-term survival after venous thromboembolism has not changed in 25 years despite some possible improvement in short-term survival. These findings have 2 important implications for future efforts to improve survival after venous thromboembolism. First, better identification of high-risk patients as well as more comprehensive and effective venous thromboembolism prophylaxis will be necessary. Second, improved therapies for patients with symptomatic pulmonary embolism are needed because of the increased risk of death compared with patients with deep vein thrombosis alone. Although pulmonary embolism and deep vein thrombosis may represent different clinical manifestations of the same disease, we believe the marked difference in survival suggests that treatment for the 2 disorders should be different and warrants investigation of alternative therapies for pulmonary embolism. We have identified baseline characteristics that can be used as predictors of both short-term and long-term survival. These predictors will be useful in directing the management of current venous thromboembolism patients as well as for the design of future clinical trials of alternative therapies.

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