Published in final edited form as: Am J Med. 2017 Feb;130(2):198-206. doi: 10.1016/j.amjmed.2016.09.008

Predictors and Causes of Long-Term Mortality in Elderly Patients with Acute Venous Thromboembolism: A Prospective Cohort Study

Nicolas Faller, MD, PhD,[a] Andreas Limacher, PhD, MAS, MSc,[b] Marie Méan, MD,[a,c] Marc Righini, MD,[d] Markus Aschwanden, MD,[e] Jürg Hans Beer, MD,[f] Beat Frauchiger, MD,[g] Josef Osterwalder, MD, MPH,[h] Nils Kucher, MD,[i] Bernhard Lämmle, MD,[j,k] Jacques Cornuz, MD, MPH,[l] Anne Angelillo-Scherrer, MD,[j] Christian M. Matter, MD,[m] Marc Husmann, MD,[n] Martin Banyai, MD,[o] Daniel Staub, MD,[e] Lucia Mazzolai, MD, PhD,[p] Olivier Hugli, MD,[q] Nicolas Rodondi, MD, MAS,[a] Drahomir Aujesky, MD, MSc[a]

[a]Department of General Internal Medicine, Bern University Hospital, University of Bern, Switzerland; [b]Clinical Trials Unit Bern, Department of Clinical Research, and Institute of Social and Preventive Medicine, University of Bern, Switzerland; [c]Division of Internal Medicine, Lausanne University Hospital, Switzerland; [d]Division of Angiology and Hemostasis, Geneva University Hospital, Switzerland; [e]Division of Angiology, Basel University Hospital, Switzerland; [f]Department of Internal Medicine, Cantonal Hospital of Baden, Switzerland; [g]Department of Internal Medicine, Cantonal Hospital of Frauenfeld, Switzerland; [h]Department of Emergency Medicine, Cantonal Hospital of St Gallen, Switzerland; [i]Division of Angiology, Bern University Hospital, Switzerland; [j]University Clinic of Hematology and Central Hematology Laboratory, Bern University Hospital, Switzerland; [k]Center for Thrombosis and Hemostasis, University Medical Center, Mainz, Germany; [l]Department of Ambulatory Care and Community Medicine, Lausanne University Hospital, Switzerland; [m]Center for Molecular Cardiology, University of Zurich, and Clinic for Cardiology, University Heart Center, Zurich University Hospital, Switzerland; [n]Division of Angiology, Zurich University Hospital, Switzerland; [o]Division of Angiology, Cantonal Hospital of Lucerne, Switzerland; [p]Division of Angiology, Lausanne University Hospital, Switzerland; [q]Emergency Department, Lausanne University Hospital, Switzerland.

ABSTRACT

BACKGROUND: Long-term predictors and causes of death are understudied in elderly patients with acute venous thromboembolism.

METHODS: We prospectively followed up 991 patients aged ≥65 years with acute venous thromboembolism in a multicenter Swiss cohort study. The primary outcome was overall mortality. We explored the association between patient baseline characteristics and mortality, adjusting for other baseline variables and periods of anticoagulation as a time-varying covariate. Causes of death over time were adjudicated by a blinded, independent committee.

RESULTS: The median age was 75 years. During a median follow-up period of 30 months, 206 patients (21%) died. Independent predictors of overall mortality were age (hazard ratio [HR], 1.32; 95% confidence interval [CI], 1.05-1.65, per decade), active cancer (HR, 5.80; 95% CI, 4.22-7.97), systolic blood pressure <100 mm Hg (HR, 2.77; 95% CI, 1.56-4.92), diabetes mellitus (HR, 1.50; 95% CI, 1.02-2.22), low physical activity level (HR, 1.92; 95% CI, 1.38-2.66), polypharmacy (HR, 1.41; 95% CI, 1.01-1.96), anemia (HR, 1.48; 95% CI, 1.07-2.05), high-sensitivity C-reactive protein >40 mg/L (HR, 1.88; 95% CI, 1.36-2.60), ultra-sensitive troponin >14 pg/mL (HR, 1.54; 95% CI, 1.06-2.25), and D-dimer >3000 ng/mL (HR, 1.45; 95% CI, 1.04-2.01). Cancer (34%), pulmonary embolism (18%), infection (17%), and bleeding (6%) were the most common causes of death.

CONCLUSIONS: Elderly patients with acute venous thromboembolism have a substantial long-term mortality, and several factors, including polypharmacy and a low physical activity level, are associated with

Funding: The study was supported by a grant of the Swiss National Science Foundation (No. 33CSCO-122659/139470).

Conflict of Interest: None.

Authorship: All authors had access to the data and played a role in writing this manuscript.

Published in final edited form as: Am J Med. 2017 Feb;130(2):198-206. doi: 10.1016/j.amjmed.2016.09.008

long-term mortality. Cancer, pulmonary embolism, infections, and bleeding are the most common causes of death in the elderly with venous thromboembolism.

KEYWORDS: Cause of death; Elderly; Mortality; Predictor; Venous thromboembolism

The incidence of venous thromboembolism increases sharply with age, with 27 cases per 100,000 person-years in persons aged ≤40 years to 410 cases in those aged ≥65 years.[1] Patients aged 65 years or more comprise more than 60% of venous thromboembolism cases occurring in the community setting.[2] The elderly not only have a higher incidence of venous thromboembolism but also have an approximately 2-fold increase in major bleeding and 2- to 3-fold greater risk of all-cause mortality over time than younger patients.[2] Despite the higher morbidity and mortality, venous thromboembolism remains understudied in the elderly,[2] and little is known about the predictors and causes of death in older patients with venous thromboembolism. Prior studies reporting predictors and causes of death in elderly patients with venous thromboembolism were limited by a retrospective design,[2-4] identified cases with venous thromboembolism using diagnosis codes rather than predefined clinical criteria,[2] failed to report causes of death,[2,5,6] or determined the cause of death without the use of a formal adjudication process.[4,7-9] Moreover, these studies almost exclusively focused on short-term mortality (<6 months),[3-5,7-9] and predictors and causes of long-term mortality remain largely unknown in the elderly with venous thromboembolism. To fill these gaps of knowledge, we aimed to examine which factors drive long-term mortality and to determine causes of death in a multicenter prospective study of elderly patients with acute venous thromboembolism using a formal mortality adjudication process.

CLINICAL SIGNIFICANCE

- Elderly patients with acute venous thromboembolism have a substantial long-term overall mortality (21%).
- Besides cancer and arterial hypotension, predictors of long-term mortality include polypharmacy and low physical activity in the elderly with venous thromboembolism.
- Most elderly patients with venous thromboembolism die of cancer, pulmonary embolism, infection, and bleeding.

MATERIALS AND METHODS

Cohort Sample

This study was conducted between September 2009 and December 2013 as part of a prospective multicenter cohort study that assessed long-term medical outcomes and quality of life in elderly patients with acute symptomatic venous thromboembolism from all 5 university and 4 high-volume nonuniversity hospitals in Switzerland (SWITCO65+).[10]

Consecutive patients aged ≥65 years with an acute, objectively confirmed venous thromboembolism were identified in the inpatient and outpatient services of all participating study sites. We defined symptomatic deep vein thrombosis as an acute onset of leg pain or swelling plus incomplete compressibility of a venous segment on ultrasonography or an intraluminal filling defect on contrast venography.[11] For iliac and caval deep vein thrombosis, abnormal duplex flow patterns compatible with thrombosis or an intraluminal filling defect on computed tomography or magnetic resonance imaging venography were used as additional diagnostic criteria.[12-14] Patients with isolated distal vein thrombosis were eligible only if the incompressible distal vein diameter was at least 5 mm.[15,16] We defined symptomatic pulmonary embolism as a positive computed tomography or pulmonary angiography, a high-probability ventilation-perfusion scan, or a proximal deep vein thrombosis confirmed by compression ultrasonography or contrast venography in patients with acute chest pain, new or worsening dyspnea, hemoptysis, or syncope.[17,18]

Exclusion criteria included inability to provide informed consent (ie, severe dementia), impossible follow-up (ie, because of terminal illness), insufficient German or French speaking ability, thrombosis at a different site than lower limb, catheter-related thrombosis, or prior enrollment in the cohort. Ethics committees at each hospital approved the study, and all patients underwent written informed consent.

Baseline Data Collection

Study nurses collected baseline demographics (age, gender), body mass index, lifestyle factors (smoking status, physical activity level), comorbidities (diabetes mellitus, arterial hypertension, active cancer, cardiac disease, cerebrovascular disease, chronic lung disease, chronic liver disease, chronic renal disease, recent major bleeding, recent major surgery, immobilization >3 days during the last 3 months, and risk of falls), vital signs (altered mental status, heart rate, temperature, respiratory rate, systolic blood pressure, and arterial oxygen saturation), laboratory findings (hemoglobin, creatinine, platelet count, ultra-sensitive troponin, N-terminal pro B-type natriuretic peptide, high-sensitivity C-reactive protein, high-sensitivity D-dimer), and treatments at the time of diagnosis (concomitant antiplatelet therapy, polypharmacy, anticoagulation before index venous thromboembolism, vitamin K antagonist therapy, and type of initial parenteral anticoagulation) using standardized data collection forms. The risk of falls was assessed using 2 validated

Published in final edited form as: Am J Med. 2017 Feb;130(2):198-206. doi: 10.1016/j.amjmed.2016.09.008

screening questions: 1) Did you fall during the last year? 2) Did you notice any problem with gait, balance, or mobility?[19] Patients who answered yes to at least 1 screening question were considered to be at high risk of falls. Polypharmacy was defined as the prescription of more than 4 drugs, including St John's wort, at the time of the index venous thromboembolism event.[20]

Study Outcome

The outcome was the time to death from all causes after the index venous thromboembolism. Follow-up included 1 telephone interview and 2 surveillance face-to-face evaluations during the first year of study participation and then semiannual contacts, alternating between telephone calls and face-to-face evaluations (clinic visits or home visits in housebound patients), as well as periodic reviews of the patients' hospital chart.[10] When death occurred, supplemental information was obtained by reviewing medical charts and interviewing patients' primary care physicians or family members. Moreover, nurses obtained information about the cause of death from hospital discharge letters and autopsy reports if available. A committee of 3 independent, blinded clinical experts classified the cause of death as definitely due to pulmonary embolism, possibly due to pulmonary embolism, due to major bleeding, or due to another cause.[10] Death was judged to be a definite, fatal pulmonary embolism if it was confirmed by autopsy or if death followed a clinically severe pulmonary embolism, either initially or after an objectively confirmed recurrent event. Death in a patient who died suddenly without obvious cause was classified as a possible, fatal pulmonary embolism. Death was judged to be bleeding related if it followed an intracranial hemorrhage or a bleeding episode leading to hemodynamic deterioration.[21] Final classifications were made on the basis of the full consensus of this committee.

Statistical Analysis

We compared baseline characteristics of patients who died and those who survived using the chi-square test and the nonparametric Wilcoxon rank-sum test as appropriate. Mortality rates were calculated for 3 periods of follow-up: 0 to 3 months, 3 to 12 months, and 12 to 36 months. Cumulative incidences and hazards of death were estimated from a flexible parametric survival model using 2 degrees of freedom for the baseline hazard function and time-constant covariates.[22] Time dependence of covariates and adequate number of degrees of freedom were explored using model comparisons.

We explored associations between patient baseline characteristics and overall mortality using Cox regression analysis, adjusting for other baseline variables and periods of anticoagulation as a time-varying covariate. Missing values were imputed using chained equations. Imputation models were based on all other variables, as well as an indicator variable for death and the duration of follow-up. In total, 20 imputed data sets were generated, which were analyzed as described earlier using Rubin's rules to combine results across data sets.[23] In a sensitivity analysis, all missing values were assumed to be normal. We also compared causes of death across time periods (0-3 months, 3-12 months, and >12 months). All analyses were performed using Stata 14 (StataCorp LP, College Station, Tex).

RESULTS

Study Sample

Of the 1003 patients initially enrolled in the cohort,[10] 8 patients refused the use of their data and 4 withdrew from the study within 1 day of enrollment, leaving a final study sample of 991 patients. Patients had a median age of 75 years, and 463 (47%) were women (**Table 1**). Overall, 687 patients (69%) had pulmonary embolism ± deep vein thrombosis, whereas 304 patients (31%) had deep vein thrombosis only. Compared with patients with deep vein thrombosis only, patients with pulmonary embolism ± deep vein thrombosis had a higher body mass index (27 vs 26 kg/m^2, $P = .01$) and were more likely to have arterial hypertension (66% vs 60%, $P = .049$), a heart rate ≥110 beats/min (12% vs 2%, $P < .001$), a respiratory rate ≥30 breaths/min (5% vs 2%, $P = .02$), an arterial oxygen saturation <90% (16% vs 3%, $P < .001$), and elevated troponin (53% vs 46%, $P = .04$), N-terminal pro B-type natriuretic peptide (66% vs 50%, $P < .001$), and C-reactive protein levels (40% vs 25%, $P < .001$), whereas patients with deep vein thrombosis only were more likely to be anemic (50% vs 39%, $P = .003$). Age, arterial hypotension, active cancer, and other comorbidities did not differ between patients with pulmonary embolism ± deep vein thrombosis and those with deep vein thrombosis only.

A total of 206 patients (21%) died during a median follow-up of 30 months (interquartile range, 19-36 months). Patients who died were older, had a lower body mass index, and were more likely to have comorbidities, including cancer, diabetes mellitus, cardiac disease, cerebrovascular disease, and chronic lung and renal disease, than those who survived (**Table 1**). They also more frequently had polypharmacy, a high risk of falls, and a low physical activity level, whereas recent major surgery was less common. Patients who died also were more likely to have arterial hypotension and a low arterial oxygen saturation on admission, as well as pathologic laboratory findings, including anemia, thrombocytopenia, and elevated creatinine, C-reactive protein, troponin, N-terminal pro B-type natriuretic peptide, and D-dimer levels.

Cumulative Incidences of Overall Mortality

Of the 206 patients who died, 53 (26%) died within the first 3 months after the index venous thromboembolism, 60 (29%) died between month 3 and 12, and 93 (45%) died after 12 months. The mortality incidence was highest during the first 3 months after the index venous thromboembolism and decreased over time (**Table 2**). Most patients died within 12 months of the index venous thromboembolism (**Figure A**). The cumulative

Published in final edited form as: Am J Med. 2017 Feb;130(2):198-206. doi: 10.1016/j.amjmed.2016.09.008

Table 1 Patient Baseline Characteristics by Survival Status

Characteristic	n (%) or Median (IQR) All (N = 991)	Patients Who Died (N = 206)	Patients Who Survived (N = 785)	*P* Value	Missing Values n (%)
Patient age (y)	75 (69-81.0)	78 (71-84)	74 (69-80)	<.001	0 (0)
Female gender	463 (47)	97 (47)	366 (47)	.91	0 (0)
BMI, kg/m^2	27 (24-30)	25 (23-28)	27 (25-30)	<.001	5 (1)
Current or past smoker	479 (48)	106 (52)	373 (48)	.26	3 (0)
PE ± DVT	687 (69)	137 (67)	550 (70)	.32	0 (0)
DVT only	304 (31)	69 (33)	235 (30)	.32	0 (0)
Diabetes mellitus	155 (16)	42 (20)	113 (14)	.04	0 (0)
Arterial hypertension	638 (64)	136 (66)	502 (64)	.58	0 (0)
Active cancer*	178 (18)	95 (46)	83 (11)	<.001	0 (0)
Cardiac disease§	118 (12)	37 (18)	81 (10)	<.01	0 (0)
Cerebrovascular disease¶	92 (9)	32 (16)	60 (8)	<.01	0 (0)
Chronic lung disease†	136 (14)	45 (22)	91 (12)	<.001	0 (0)
Chronic liver disease‡	14 (1)	4 (2)	10 (1)	.47	0 (0)
Chronic renal disease‖	185 (19)	52 (25)	133 (17)	<.01	0 (0)
Prior VTE	283 (29)	51 (25)	232 (30)	.18	0 (0)
Recent major bleeding#	47 (5)	13 (6)	34 (4)	.23	0 (0)
Recent major surgery**	149 (15)	21 (10)	128 (16)	.03	0 (0)
Immobilization >3 d during the last 3 mo	219 (22)	49 (24)	170 (22)	.51	0 (0)
High risk of fall††	457 (46)	119 (58)	338 (43)	<.001	2 (0)
Low physical activity‡‡	367 (37)	122 (60)	245 (31)	<.001	3 (0)
Altered mental status	41 (4)	8 (4)	33 (4)	.83	3 (0)
Heart rate ≥110 beats/min	88 (9)	23 (11)	65 (8)	.22	22 (2)
Temperature <36°C	70 (8)	17 (9)	53 (7)	.45	77 (8)
Respiratory rate ≥30 breaths/min	33 (4)	10 (6)	23 (4)	.23	207 (21)
Systolic BP <100 mm Hg	35 (4)	16 (8)	19 (2)	<.001	18 (2)
Arterial oxygen saturation <90%	107 (14)	31 (19)	76 (13)	.04	230 (23)
Anemia§§	388 (42)	123 (62)	265 (36)	<.001	63 (6)
Creatinine >1.5 mg/dL	99 (11)	30 (15)	69 (10)	.03	79 (8)
Platelet count <150 g/L	140 (15)	42 (21)	98 (13)	<.01	63 (6)
us cTnT >14 pg/mL	439 (51)	125 (69)	314 (46)	<.001	129 (13)
NT-proBNP >300 pg/mL	525 (61)	143 (79)	382 (56)	<.001	129 (13)
hs-CRP >40 mg/L	308 (36)	87 (48)	221 (32)	<.001	124 (13)
D-dimer >3000 ng/mL	332 (39)	81 (46)	251 (38)	.04	148 (15)
Concomitant antiplatelet therapy‖‖	321 (32)	76 (37)	245 (31)	.12	0 (0)
Polypharmacy¶¶	504 (51)	138 (67)	366 (47)	<.001	0 (0)
Anticoagulation before index VTE	51 (5)	14 (7)	37 (5)	.23	0 (0)
Parenteral anticoagulation				.010	
LMWH	465 (47)	89 (43)	376 (48)	.23	
UFH	333 (34)	83 (40)	250 (32)	.02	
Fondaparinux	158 (16)	23 (11)	135 (17)	.04	
Danaparoid	1 (0)	1 (0)	0 (0)	-	
None	34 (3)	10 (5)	24 (3)	.21	

incidence of death did not differ between patients with pulmonary embolism ± deep vein thrombosis and those with deep vein thrombosis only (**Figure B**), whereas patients with cancer had a substantially higher cumulative incidence of death than patients without cancer (**Figure C**).

Predictors of Overall Mortality

Active cancer (adjusted hazard ratio [HR], 5.80; 95% confidence interval [CI], 4.22-7.97) was the strongest predictor of overall mortality, followed by arterial hypotension (HR, 2.77; 95% CI, 1.56-4.92) (**Table 3**). Other predictors of mortality were age (HR, 1.32; 95% CI, 1.05-1.65, per decade), diabetes mellitus (HR, 1.50; 95% CI, 1.02-2.22), a low physical activity level (HR, 1.92; 95% CI, 1.38-2.66), polypharmacy (HR, 1.41; 95% CI, 1.01-1.96), anemia (HR, 1.48; 95% CI, 1.07-2.05), C-reactive protein >40 mg/L (HR, 1.88; 95% CI, 1.36-2.60), troponin >14 pg/mL (HR, 1.54; 95% CI, 1.06-2.25), and D-dimer >3000 ng/mL (HR, 1.45; 95% CI, 1.04-2.01). Body mass

Published in final edited form as: Am J Med. 2017 Feb;130(2):198-206. doi: 10.1016/j.amjmed.2016.09.008

Table 1 Continued

Characteristic	n (%) or Median (IQR) All (N = 991)	Patients Who Died (N = 206)	Patients Who Survived (N = 785)	*P* Value	Missing Values n (%)
VKA therapy	861 (87)	129 (63)	732 (93)	<.001	0 (0)
Inferior vena cava filter	11 (1)	3 (1)	8 (1)	.59	0 (0)
Thrombolysis##	30 (3)	6 (3)	24 (3)	.91	0 (0)

BMI = body mass index; BP = blood pressure; DVT = deep venous thrombosis; hs-CRP = high-sensitivity C-reactive protein; IQR = interquartile range; LMWH = low-molecular-weight heparin; NT-proBNP = N-terminal pro B-type natriuretic peptide; PE = pulmonary embolism; UFH = unfractionated heparin; us-cTnT = ultra-sensitive cardiac troponin; VKA = vitamin K antagonist; VTE = venous thromboembolism.

*Solid or hematologic cancer requiring chemotherapy, radiotherapy, surgery, or palliative care during the last 3 months.

†Known chronic obstructive pulmonary disease, interstitial lung disease, pulmonary hypertension, or bronchiectasis.

‡Liver cirrhosis, chronic hepatitis, chronic liver failure, or hemochromatosis.

§Acute heart failure during the last 3 months, a known history of systolic or diastolic heart failure, left or right heart failure, forward or backward heart failure, left ventricular ejection fraction <40%, or a myocardial infarction during the last 3 months.

‖Diabetic or hypertensive nephropathy, chronic glomerulonephritis or interstitial nephritis, myeloma-related nephropathy, or cystic kidney disease.

¶History of ischemic or hemorrhagic stroke with hemiparesis, hemiplegia, or paraplegia at the time of screening.

#Any bleeding leading to a hospital admission or red blood cell transfusions during the last 3 months.

**Within 3 months of the index venous thromboembolism.

††Based on self-report (fall during the previous year or any subjective problem with gait, balance, or mobility).

‡‡Based on self-report ("I am mostly sitting or lying, do not move a lot" or "I often walk but I avoid climbing stairs or carrying light weight").

§§Serum hemoglobin concentration <13 g/dL for men or <12 g/dL for women.

‖‖Use of aspirin, clopidogrel, prasugrel, or aspirin/dipyridamole.

¶¶Prescription of >4 drugs, including St John's wort. The intake of vitamins or alternative medicine was not considered.

##Catheter-directed or systemic thrombolysis.

index (HR, 0.93; 95% CI, 0.90-0.96) and recent major surgery (HR, 0.34; 95% CI, 0.19-0.59) were inversely associated with mortality.

Table 2 Mortality Rates

	Patients (n)	Deaths per 100 Patient-Y (95% CI)
All patients		
0-3 mo	991	22.2 (17.0-29.1)
3-12 mo	925	9.2 (7.1-11.8)
12-36 mo	841	6.4 (5.1-7.9)
Patients with PE ± DVT		
0-3 mo	687	23.7 (17.3-32.5)
3-12 mo	637	10.5 (7.9-14.0)
12-36 mo	575	5.1 (3.8-6.9)
Patients with DVT only		
0-3 mo	304	19.0 (11.2-32.0)
3-12 mo	288	6.3 (3.6-10.8)
12-36 mo	266	9.1 (6.6-12.6)
Patients with cancer		
0-3 mo	178	81.6 (57.7-115.3)
3-12 mo	142	39.2 (28.1-54.6)
12-36 mo	106	21.0 (14.5-30.3)
Patients without cancer		
0-3 mo	813	10.6 (6.9-16.2)
3-12 mo	783	4.4 (3.0-6.5)
12-36 mo	735	4.6 (3.5-6.1)

CI = confidence interval; DVT = deep venous thrombosis; PE = pulmonary embolism; VTE = venous thromboembolism.

A separate analysis showed that mortality predictors somewhat differed by type of venous thromboembolism (Table 3). Diabetes, low physical activity, anemia, and elevated cardiac biomarkers were associated with mortality only in patients with pulmonary embolism ± deep vein thrombosis, whereas age and polypharmacy were statistically significant predictors of death only in patients with isolated deep vein thrombosis.

Overall, we observed relatively few missing values (Table 1). When missing values were assumed to be normal in a sensitivity analysis, the results did not change markedly (data not shown).

Causes of Death

The cause of death could be determined in 185 patients (90%) (Table 4). Overall, 70 patients (34%) died of cancer, 36 patients (18%) died of definite or possible pulmonary embolism, 34 patients (17%) died of infection, and 13 patients (6%) died of bleeding complications. Among patients who died during the first 3 months of the index venous thromboembolism, the main causes of death were cancer (38%), definite/possible pulmonary embolism (26%), and infection (13%). Cancer remained the leading cause of death during the entire follow-up period. During the first 12 months, definite/possible pulmonary embolism and bleeding represented the second and fourth leading causes of death, respectively. Although definite/possible pulmonary embolism and bleeding remained important causes of death during long-term follow-up, the proportion of patients who died of infections and cardiac diseases increased over time.

Published in final edited form as: Am J Med. 2017 Feb;130(2):198-206. doi: 10.1016/j.amjmed.2016.09.008

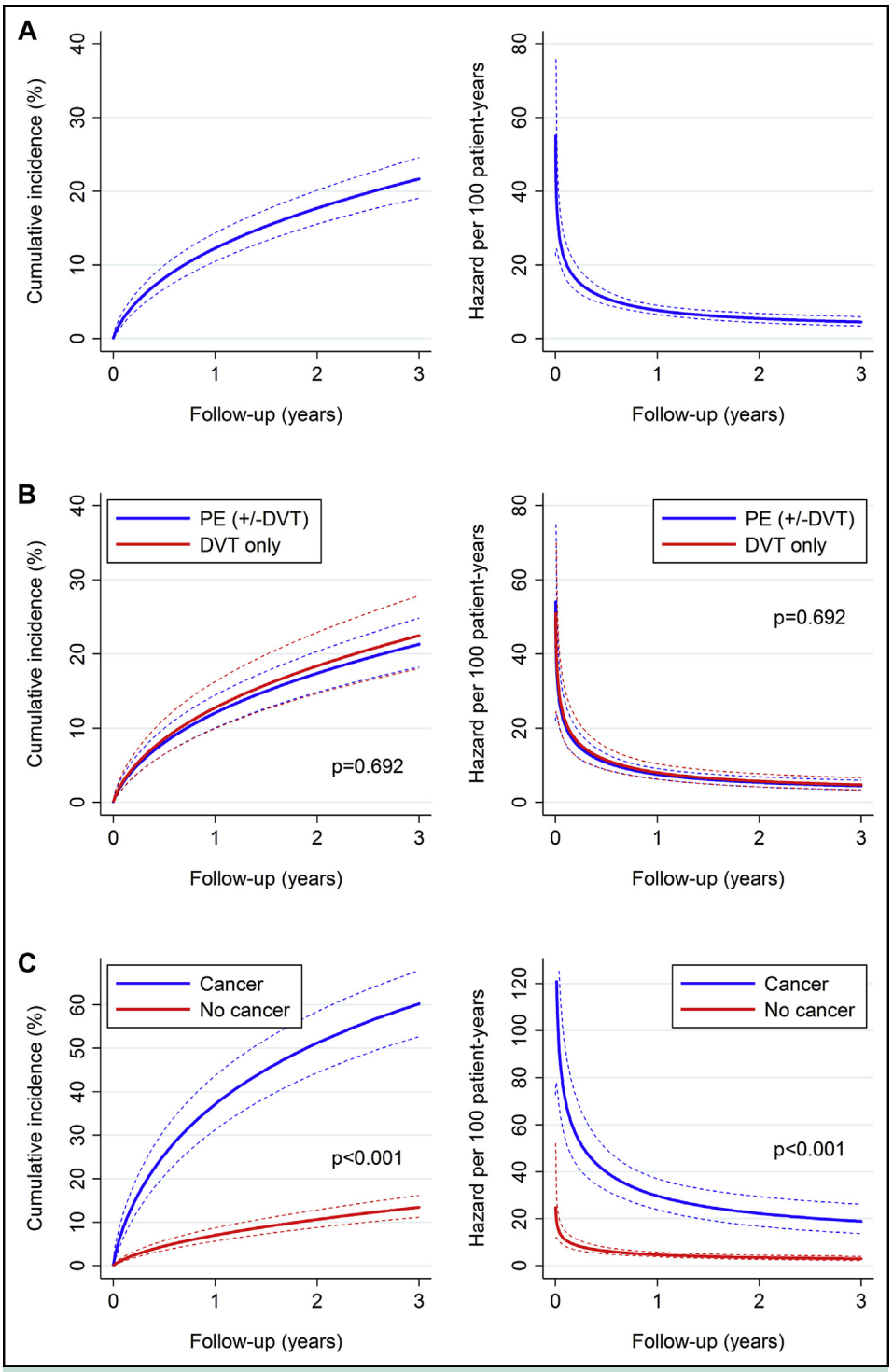

Figure Cumulative incidences and hazards of death. (**A**) Overall cumulative incidence and hazard of death. The 3-year cumulative incidence of death was 21.7%. *Dashed lines* indicate the upper and lower boundary of the 95% CI. (**B**) Cumulative incidences and hazards of death by type of index venous thromboembolism. The 3-year cumulative incidence of death was 21.3% for patients with pulmonary embolism ± deep vein thrombosis and 22.5% for patients with deep vein thrombosis only ($P = .692$ based on a Wald test). *Dashed lines* indicate the upper and lower boundary of the 95% CI. (**C**) Cumulative incidences and hazards of death by cancer status. The 3-year cumulative incidence of death was 60.2% for patients with cancer and 13.4% for patients without cancer ($P < .001$ based on a Wald test). *Dashed lines* indicate the upper and lower boundary of the 95% CI. DVT = deep vein thrombosis; PE = pulmonary embolism.

Published in final edited form as: Am J Med. 2017 Feb;130(2):198-206. doi: 10.1016/j.amjmed.2016.09.008

Table 3 Predictors of Mortality

	Adjusted* HR (95% CI)		
Predictors	All Patients (n = 991)	PE ± DVT (n = 687)	DVT Only (n = 304)
Age (per decade)	1.32 (1.05-1.65)	1.12 (0.84-1.50)	2.00 (1.27-3.14)
Female gender	0.96 (0.68-1.36)	0.85 (0.56-1.31)	1.29 (0.65-2.55)
BMI >30 kg/m^2	0.93 (0.90-0.96)	0.91 (0.87-0.95)	0.89 (0.83-0.95)
Current or past smoker	0.93 (0.66-1.29)	0.87 (0.58-1.31)	1.14 (0.58-2.23)
Diabetes mellitus	1.50 (1.02-2.22)	1.62 (1.02-2.58)	1.61 (0.71-3.66)
Arterial hypertension	0.94 (0.68-1.31)	1.02 (0.66-1.56)	0.63 (0.33-1.20)
Active cancer	5.80 (4.22-7.97)	4.84 (3.25-7.23)	13.44 (6.68-27.06)
Cardiac disease	1.37 (0.92-2.03)	1.44 (0.87-2.37)	1.81 (0.79-4.16)
Cerebrovascular disease	1.29 (0.85-1.96)	1.62 (0.95-2.76)	0.53 (0.22-1.30)
Chronic lung disease	1.26 (0.86-1.85)	1.40 (0.90-2.17)	0.77 (0.25-2.38)
Chronic liver disease	0.77 (0.26-2.22)	1.81 (0.50-6.61)	0.10 (0.01-1.20)
Chronic renal disease	1.05 (0.71-1.54)	1.04 (0.63-1.72)	1.43 (0.67-3.08)
Prior VTE	1.10 (0.78-1.57)	1.19 (0.77-1.84)	0.93 (0.47-1.83)
Recent major bleeding	0.70 (0.36-1.36)	0.73 (0.35-1.53)	0.21 (0.02-2.06)
Recent major surgery	0.34 (0.19-0.59)	0.26 (0.13-0.54)	0.34 (0.13-0.92)
Immobilization during the last 3 mo	0.94 (0.63-1.41)	0.74 (0.46-1.22)	1.53 (0.70-3.35)
Polypharmacy	1.41 (1.01-1.96)	1.31 (0.86-1.98)	2.96 (1.48-5.91)
High risk of fall	1.04 (0.76-1.43)	1.01 (0.68-1.52)	1.23 (0.61-2.49)
Low physical activity	1.92 (1.38-2.66)	2.37 (1.56-3.61)	1.12 (0.58-2.16)
PE as the index event	1.17 (0.84-1.63)	NA	NA
Altered mental status	0.63 (0.29-1.35)	0.58 (0.21-1.63)	0.44 (0.11-1.82)
Heart rate ≥110 beats/min	0.91 (0.54-1.53)	0.78 (0.44-1.39)	2.06 (0.30-14.26)
Temperature <36°C	1.09 (0.62-1.92)	1.40 (0.73-2.68)	0.65 (0.20-2.14)
Respiratory rate ≥30 breaths/min	1.69 (0.90-3.20)	1.74 (0.83-3.62)	1.30 (0.20-8.55)
Systolic BP <100 mm Hg	2.77 (1.56-4.92)	2.51 (1.19-5.28)	7.79 (2.04-29.66)
Arterial oxygen saturation <90%	1.26 (0.80-1.99)	1.35 (0.82-2.23)	0.84 (0.12-5.93)
Anemia	1.48 (1.07-2.05)	1.61 (1.09-2.39)	1.37 (0.65-2.93)
Creatinine >1.5 mg/dL	0.86 (0.53-1.39)	0.77 (0.42-1.40)	1.20 (0.42-3.49)
Platelet count <150 g/L	1.28 (0.89-1.85)	1.07 (0.66-1.73)	1.94 (0.93-4.07)
us cTnT >14 pg/mL	1.54 (1.06-2.25)	2.18 (1.32-3.58)	0.60 (0.28-1.27)
NT-proBNP >300 pg/mL	1.35 (0.89-2.06)	1.48 (0.85-2.59)	1.26 (0.56-2.87)
hs-CRP >40 mg/L	1.88 (1.36-2.60)	2.02 (1.35-3.03)	1.50 (0.76-2.97)
D-dimer >3000 ng/mL	1.45 (1.04-2.01)	1.47 (0.97-2.24)	1.39 (0.73-2.65)

BMI = body mass index; BP = blood pressure; CI = confidence interval; DVT = deep venous thrombosis; HR = hazard ratio; hs-CRP = high-sensitivity C-reactive protein; NA = not applicable; NT-proBNP = N-terminal pro B-type natriuretic peptide; PE = pulmonary embolism; us-cTnT = ultra-sensitive cardiac troponin; VTE = venous thromboembolism.

*Adjustments were made for all other baseline variables.

DISCUSSION

Our results show that elderly patients with acute venous thromboembolism have a substantial long-term mortality (21%) and that several clinical factors (age, diabetes, cancer, polypharmacy, low physical activity, systolic hypotension) and laboratory abnormalities (anemia and elevated troponin, C-reactive protein, and D-dimer) are associated with an increased risk of long-term mortality. Cancer, pulmonary embolism, infections, and bleeding are the most common causes of death in the elderly with venous thromboembolism.

Prior retrospective and prospective studies that examined predictors of 3-year mortality in older patients with venous thromboembolism found an episode of major bleeding after the index venous thromboembolism and age ≥80 years to be predictors of all-cause mortality.[2,6] The remaining studies examining predictors of death in the elderly with venous thromboembolism focused exclusively on short-term mortality (<6 months) in patients with pulmonary embolism, the more severe form of venous thromboembolism.[3-5,8] These studies demonstrated that comorbid burden, cancer, cardiovascular and neurodegenerative diseases, chronic lung disease, arterial hypotension, hypoxemia, thrombocytopenia, and elevated cardiac troponins were associated with all-cause mortality.[3-5,8] Our study extends the existing knowledge by identifying several additional factors that are associated with long-term mortality in the elderly with acute venous thromboembolism. In addition to age, cancer, arterial hypotension, and several laboratory abnormalities at the time of admission, our study also identified polypharmacy and a low level of physical activity as predictors of long-term mortality in the elderly with venous thromboembolism. Both polypharmacy and a low physical activity level were previously shown to be

Published in final edited form as: Am J Med. 2017 Feb;130(2):198-206. doi: 10.1016/j.amjmed.2016.09.008

Table 4 Causes of Death

Cause of Death	n (%) All Deaths (N = 206)	Deaths 0-3 Mo (N = 53)	Deaths 3-12 Mo (N = 60)	Deaths >12 Mo (N = 93)	*P* Value
Cancer	70 (34)	20 (38)	28 (47)	22 (24)	.064
Definite or possible PE	36 (18)	14 (26)	8 (13)	14 (15)	
Infection	34 (17)	7 (13)	7 (12)	20 (22)	
Bleeding	13 (6)	3 (6)	5 (8)	5 (5)	
Left ventricular failure	13 (6)	2 (4)	3 (5)	8 (9)	
Pulmonary causes	7 (3)	2 (4)	4 (7)	1 (1)	
Acute coronary syndrome	3 (2)	1 (2)	0 (0)	2 (2)	
Suicide	3 (2)	0 (0)	0 (0)	3 (3)	
Ischemic stroke	2 (1)	0 (0)	0 (0)	2 (2)	
Other*	4 (2)	0 (0)	2 (3)	2 (2)	
Unknown	21 (10)	4 (8)	3 (5)	14 (15)	

PE = pulmonary embolism.
*Trauma (n = 1), renal failure (n = 1), decompensated liver cirrhosis (n = 1), and peripheral artery occlusive disease (n = 1).

associated with a higher risk of bleeding in older patients with venous thromboembolism, possibly as a consequence of a higher risk of falls and comorbid burden.[24,25] Whether the reduction of polypharmacy or an increase in physical activity has the potential to improve survival in the elderly with venous thromboembolism should be further examined.

Of note, in contrast to a prior study from the 1980s that demonstrated a higher mortality in elderly patients presenting with pulmonary embolism compared with deep vein thrombosis,[26] our results did not show a mortality difference between patients with pulmonary embolism ± deep vein thrombosis and those with deep vein thrombosis only, despite the fact that patients with pulmonary embolism ± deep vein thrombosis had more signs of acute physiologic derangement (tachycardia, tachypnea, hypoxemia) and right ventricular dysfunction (elevated troponin and N-terminal pro B-type natriuretic peptide values) at the time of diagnosis. A potential explanation is that short- and long-term prognoses of elderly patients with venous thromboembolism may be driven by comorbid diseases than by the severity of the initial venous thromboembolism event.[6] Moreover, as shown in a Danish cohort study, the 30-day mortality rate ratios for pulmonary embolism, compared with patients without venous thromboembolism, declined markedly from 138 in 1980 to 1989 to 36 in 2000 to 2011 for pulmonary embolism, possibly because of the use of improved diagnostic imaging with detection of less severe pulmonary embolism and improvement in the treatment of pulmonary embolism.[27]

To our knowledge, no prior study examined long-term causes of death in elderly patients with venous thromboembolism. In our study, cancer was the most common cause of death over time. Although pulmonary embolism remained the second leading cause of death during the first 12 months, other causes of death (infections, cardiovascular causes) became more common after 12 months of follow-up. The proportion of patients who died of bleeding remained fairly constant over time (5%-8%).

Overall, 26% of patients died of definite or possible pulmonary embolism during the first 3 months in our cohort. Our results are consistent with 2 prior studies demonstrating that the proportion of octogenarians and nonagenarians who died of pulmonary embolism within 3 months of the index venous thromboembolism was 27% and 32%, respectively.[7,9] Other studies showed that the proportion of older patients with pulmonary embolism who died of pulmonary embolism decreased with increasing length of follow-up and varied from 91% in patients who died in the hospital to 21% in patients who died within 6 months.[3,4,8]

In times of declining autopsy rates, cause-of-death ascertainment is challenging in patients with venous thromboembolism. We used a committee of independent and blinded clinical experts to adjudicate causes of death, with the final adjudication based on the full consensus of the committee. In prior studies reporting cause of death in the elderly with venous thromboembolism, causes of death were assigned by unblinded attending physicians[7,9] or based on death certificates only,[3] or the method of ascertaining cause of death was not specified.[4,8] Evidence suggests significantly exaggerated treatment effects in clinical trials with nonblinded versus blinded assessors for binary and scale measurement outcomes,[28,29] and cause-of-death ascertainment based on death certificates may substantially differ from autopsy findings.[30] To reduce the risk of ascertainment bias, the use of adjudication committees has been advocated and quality criteria for planning and reporting such committees have been established,[31] including the type of information provided to the committee, the blinding/independence of the committee members, and the method of reaching a final decision.

Study Limitations

Our study has potential limitations. First, the cohort used for this analysis excluded patients with severe dementia or terminal illness,[10] which may have led to an underestimation of

mortality. Indeed, the Worcester Venous Thromboembolism Study reported a 3-year mortality of 37% in older patients compared with 21% in our study.[6] Second, our cohort included patients aged ≥65 years only, and we could not compare predictors and causes of death in older versus younger patients. Finally, we can only detect associations, not causality, from these data. Thus, we cannot determine whether the clinical and laboratory factors associated with mortality (ie, age, diabetes, cancer, polypharmacy, low physical activity, anemia, and elevated C-reactive protein) have a specific effect on the pathophysiology of pulmonary embolism or whether they are simply markers of adverse outcome.

CONCLUSIONS

Our prospective multicenter cohort study provides new insight into long-term predictors and causes of death in elderly patients with venous thromboembolism, an understudied clinical area. Several clinical factors that are highly prevalent among the elderly, including cancer, polypharmacy, and low physical activity, were associated with an increased risk of long-term mortality. Cancer, pulmonary embolism, infections, and bleeding were the most common causes of death.

ACKNOWLEDGMENT

The authors thank all the collaborators of the SWITCO65+ study.

References

1. Naess IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerstrom J. Incidence and mortality of venous thrombosis: a population-based study. *J Thromb Haemost*. 2007;5:692-699.
2. Spencer FA, Gore JM, Lessard D, et al. Venous thromboembolism in the elderly. A community-based perspective. *Thromb Haemost*. 2008;100:780-788.
3. Moutzouris JP, Chow V, Yong AS, et al. Acute pulmonary embolism in individuals aged 80 and older. *J Am Geriatr Soc*. 2014;62:2004-2006.
4. de Bonis S, Rendina D, Vargas G, et al. Predictors of in-hospital and long-term clinical outcome in elderly patients with massive pulmonary embolism receiving thrombolytic therapy. *J Am Geriatr Soc*. 2008;56:2273-2277.
5. Spirk D, Husmann M, Hayoz D, et al. Predictors of in-hospital mortality in elderly patients with acute venous thrombo-embolism: the SWIss Venous ThromboEmbolism Registry (SWIVTER). *Eur Heart J*. 2012;33:921-926.
6. Spencer FA, Gurwitz JH, Schulman S, et al. Venous thromboembolism in older adults: a community-based study. *Am J Med*. 2014;127:530-537e3.
7. Vasco B, Villalba JC, Lopez-Jimenez L, et al. Venous thromboembolism in nonagenarians. Findings from the RIETE Registry. *Thromb Haemost*. 2009;101:1112-1118.
8. Castelli R, Bucciarelli P, Porro F, Depetri F, Cugno M. Pulmonary embolism in elderly patients: prognostic impact of the Cumulative Illness Rating Scale (CIRS) on short-term mortality. *Thromb Res*. 2014;134:326-330.
9. Lopez-Jimenez L, Montero M, Gonzalez-Fajardo JA, et al. Venous thromboembolism in very elderly patients: findings from a prospective registry (RIETE). *Haematologica*. 2006;91:1046-1051.
10. Mean M, Righini M, Jaeger K, et al. The Swiss cohort of elderly patients with venous thromboembolism (SWITCO65+): rationale and methodology. *J Thromb Thrombolysis*. 2013;36:475-483.
11. Dauzat M, Laroche JP, Deklunder G, et al. Diagnosis of acute lower limb deep venous thrombosis with ultrasound: trends and controversies. *J Clin Ultrasound*. 1997;25:343-358.
12. Enden T, Sandvik L, Klow NE, et al. Catheter-directed Venous Thrombolysis in acute iliofemoral vein thrombosis—the CaVenT study: rationale and design of a multicenter, randomized, controlled, clinical trial (NCT00251771). *Am Heart J*. 2007;154:808-814.
13. Fraser DG, Moody AR, Davidson IR, Martel AL, Morgan PS. Deep venous thrombosis: diagnosis by using venous enhanced subtracted peak arterial MR venography versus conventional venography. *Radiology*. 2003;226:812-820.
14. Fraser DG, Moody AR, Morgan PS, Martel AL, Davidson I. Diagnosis of lower-limb deep venous thrombosis: a prospective blinded study of magnetic resonance direct thrombus imaging. *Ann Intern Med*. 2002;136:89-98.
15. Kearon C, Ginsberg JS, Hirsh J. The role of venous ultrasonography in the diagnosis of suspected deep venous thrombosis and pulmonary embolism. *Ann Intern Med*. 1998;129:1044-1049.
16. Righini M, Paris S, Le Gal G, Laroche JP, Perrier A, Bounameaux H. Clinical relevance of distal deep vein thrombosis. Review of literature data. *Thromb Haemost*. 2006;95:56-64.
17. Buller HR, Davidson BL, Decousus H, et al. Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. *N Engl J Med*. 2003;349:1695-1702.
18. Le Gal G, Righini M, Sanchez O, et al. A positive compression ultrasonography of the lower limb veins is highly predictive of pulmonary embolism on computed tomography in suspected patients. *Thromb Haemost*. 2006;95:963-966.
19. Ganz DA, Bao Y, Shekelle PG, Rubenstein LZ. Will my patient fall? *JAMA*. 2007;297:77-86.
20. Gasse C, Hollowell J, Meier CR, Haefeli WE. Drug interactions and risk of acute bleeding leading to hospitalisation or death in patients with chronic atrial fibrillation treated with warfarin. *Thromb Haemost*. 2005;94:537-543.
21. Jakobsson C, Jimenez D, Gomez V, Zamarro C, Mean M, Aujesky D. Validation of a clinical algorithm to identify low-risk patients with pulmonary embolism. *J Thromb Haemost*. 2010;8:1242-1247.
22. Royston P, Lambert P. *Flexible Parametric Survival Analysis Using Stata: Beyond the Cox Model*. College Station, TX: Stata Press; 2011.
23. Rubin D. *Multiple Imputation for Nonresponse in Surveys*. New York: John Wiley & Sons; 1987.
24. Leiss W, Mean M, Limacher A, et al. Polypharmacy is associated with an increased risk of bleeding in elderly patients with venous thromboembolism. *J Gen Intern Med*. 2015;30:17-24.
25. Frey PM, Mean M, Limacher A, et al. Physical activity and risk of bleeding in elderly patients taking anticoagulants. *J Thromb Haemost*. 2015;13:197-205.
26. Kniffin WD Jr, Baron JA, Barrett J, Birkmeyer JD, Anderson FA Jr. The epidemiology of diagnosed pulmonary embolism and deep venous thrombosis in the elderly. *Arch Intern Med*. 1994;154:861-866.
27. Sogaard KK, Schmidt M, Pedersen L, Horvath-Puho E, Sorensen HT. 30-year mortality after venous thromboembolism: a population-based cohort study. *Circulation*. 2014;130:829-836.
28. Hrobjartsson A, Thomsen AS, Emanuelsson F, et al. Observer bias in randomized clinical trials with measurement scale outcomes: a systematic review of trials with both blinded and nonblinded assessors. *CMAJ*. 2013;185:E201-E211.
29. Hrobjartsson A, Thomsen AS, Emanuelsson F, et al. Observer bias in randomised clinical trials with binary outcomes: systematic review of trials with both blinded and non-blinded outcome assessors. *BMJ*. 2012;344:e1119.
30. Smith Sehdev AE, Hutchins GM. Problems with proper completion and accuracy of the cause-of-death statement. *Arch Intern Med*. 2001;161:277-284.
31. Dechartres A, Boutron I, Roy C, Ravaud P. Inadequate planning and reporting of adjudication committees in clinical trials: recommendation proposal. *J Clin Epidemiol*. 2009;62:695-702.