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Full Length Article

Anticoagulation quality and clinical outcomes in multimorbid elderly patients with acute venous thromboembolism☆

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ABSTRACT

Background: Multimorbid patients with acute venous thromboembolism (VTE) are often excluded from clinical trials and little is known about their prognosis.
Objectives: To examine whether multimorbidity is associated with adverse clinical outcomes and lower anticoagulation quality in older patients with VTE.
Patients/Methods: We studied 991 patients aged ≥65 years with acute VTE in a Swiss prospective multicenter cohort study. A modified Charlson Comorbidity Index was used to measure multimorbidity, which was defined as the presence ≥2 of 17 predefined comorbid conditions. We examined the association between multimorbidity and recurrent VTE and major bleeding, adjusting for confounders and periods of anticoagulation. We assessed whether the percentage of time spent in the therapeutic international normalized ratio (INR) range varied by the number of comorbidities present.
Results: Overall, 708 (71%) patients were multimorbid. Multimorbid patients had a higher 3-year cumulative incidence of recurrent VTE (16.8 vs. 10.8%; $P = 0.056$) and major bleeding (18.7 vs. 9.0%; $P = 0.001$) than non-multimorbid patients. After adjustment, multimorbid patients had a significantly higher risk of recurrent VTE (sub-hazard ratio [SHR] 1.66, 95% confidence interval [CI] 1.08–2.57) and a higher risk of major bleeding (SHR 1.55, 95% CI 0.96–2.50), although the latter failed to achieve statistical significance. With increasing numbers of comorbid conditions, patients spent less time in and more time above and below the therapeutic INR range.
Conclusions: Multimorbid patients with acute VTE have not only a lower anticoagulation quality but also more complications. Clinical trials should explicitly enroll multimorbid patients to determine the optimal anticoagulation strategy in such patients.

1. Introduction

Acute venous thromboembolism (VTE) is not only more common in the elderly, rates of mortality and major bleeding in older patients with VTE are also two times higher than those in younger patients [1]. Multimorbidity, commonly defined as the co-occurrence of two or more chronic comorbidities, affects the majority of elderly persons [2–6]. According to a previous study, 65% of the general population aged 65–84 years are multimorbid, with the prevalence rising to 82% in those aged > 85 years [2].

Evidence suggests that patients with a greater burden of comorbidities appear to spend less time within the therapeutic international normalized ratio (INR) range [7,8], resulting in a lower quality of anticoagulation therapy. In a retrospective cohort study, the presence of three or more comorbidities predicted serious anticoagulation-related bleeding in a patient group with mixed indications for oral anticoagulation [9]. Moreover, the risk of short- and long-term mortality increases with the cumulative number of comorbid conditions in patients with VTE [10–13].

Prior evidence on the benefit/risks of anticoagulation in multimorbid patients is relatively scarce and has primarily focused on conditions other than VTE [9] or did not address relevant clinical outcomes, such as recurrent VTE or major bleeding [7,8]. Patients with comorbid conditions are also underrepresented in clinical

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anticoagulation trials and the prognosis of multimorbid patients with VTE is not well known [14]. To fill this gap of knowledge, we examined the association between multimorbidity and clinical outcomes in elderly patients with acute VTE in a large prospective multicenter cohort study. We also compared the quality of anticoagulation between multimorbid and non-multimorbid patients treated with vitamin K antagonists.

2. Methods

2.1. Participants and setting

The study was conducted between September 2009 and December 2013 as part of the SWIss venous Thromboembolism COhort (SWITCO65+), a prospective multicenter cohort study that assessed long-term medical outcomes and quality of life in elderly patients with VTE from all five university and four high-volume hospitals in Switzerland. Consecutive patients aged ≥65 years with acute, objectively confirmed symptomatic deep vein thrombosis (DVT) and/or pulmonary embolism (PE) were identified in the in- and outpatient services of all participating study sites. Exclusion criteria were catheter-related thrombosis, thrombosis at a different site than lower limb, conditions incompatible with follow-up (i.e., life expectancy < 3 months), inability to provide informed consent (i.e., severe dementia), or insufficient French- or German-speaking ability. A detailed description of the study methods was published elsewhere [15]. All participants provided written informed consent. The study was approved by the institutional review board at each participating site.

2.2. Data collection

Trained study nurses recorded baseline sociodemographic and personal characteristics (age, sex, body weight, height), initial site of treatment (in- or outpatient), history of major bleeding and VTE, recent major surgery, comorbid conditions (arterial hypertension, alcohol abuse, inflammatory bowel disease, active cancer, coronary heart disease, congestive heart failure, cerebrovascular disease, hemi-/paraplegia, peripheral arterial disease, active rheumatic disease, diabetes mellitus, and chronic pulmonary, renal and liver diseases), location of index VTE (PE ± DVT, DVT only), laboratory findings (hemoglobin concentration and platelet count), concomitant treatment with antiplatelet or non-steroidal anti-inflammatory drugs (NSAIDs), and VTE-related treatments (unfractionated heparin, low-molecular-weight heparin, fondaparinux, danaparoid, vitamin K antagonists, thrombolysis, thrombembolectomy, inferior vena cava filter) from all enrolled patients using standardized data collection forms.

2.3. Comorbidity and multimorbidity measures

No commonly accepted method exists to assess comorbid burden in patients with VTE or other diseases [3,16,17]. We measured comorbidity using a modified, unweighted Charlson Comorbidity Index (mCCI) [18]. We omitted three variables from the original index (AIDS, peptic ulcer disease, and dementia) and did not include disease severity (mild vs. moderate/severe kidney and liver disease, diabetes with or without end-organ failure) because this information was not recorded in the SWITCO65+ database. We added several conditions (anemia, alcohol abuse, inflammatory bowel disease, obesity, arterial hypertension) that are commonly used in comorbidity assessments [19] and are known to be associated with VTE recurrence [20–23], bleeding [24,25], or anticoagulation quality [26,27]. Finally, we simplified the original index by aggregating the cancer-related variables (leukemia, lymphoma, solid tumor with or without metastasis) into two variables (active cancer and metastatic cancer). The final mCCI comprised 17 variables (Table 1), with a score range between 0 and 17 points (1 point per variable present). For the purpose of this study, we defined multimorbidity as the presence of two or more conditions based on the mCCI [17].

Table 1
Prevalence of comorbid conditions based on the modified Charlson Comorbidity Index in elderly patients with VTE.

Comorbid condition*	Patients (*N* = 991)	Multimorbid† (*N* = 708)	Non-multimorbid (*N* = 283)
	n (%)		
Arterial hypertension‡	638 (64)	554 (78)	84 (30)
Anemia§	388 (42)	357 (52)	31 (13)
Obesity¶	242 (25)	225 (32)	17 (6)
Chronic renal disease**	185 (19)	180 (25)	5 (2)
Active cancer††	178 (18)	172 (24)	6 (2)
Coronary heart disease‡‡	172 (17)	166 (23)	6 (2)
Diabetes mellitus§§	155 (16)	149 (21)	6 (2)
Chronic pulmonary disease¶¶	136 (14)	131 (19)	5 (2)
Congestive heart failure***	115 (12)	112 (16)	3 (1)
Alcohol abuse†††	100 (10)	82 (12)	18 (6)
Cerebrovascular disease‡‡‡	92 (9)	88 (12)	4 (1)
Peripheral arterial disease	69 (7)	68 (10)	1 (0)
Metastatic solid cancer	72 (7)	72 (10)	0 (0)
Active rheumatic disease§§§	32 (3)	28 (4)	4 (1)
Hemi−/paraplegia¶¶¶	29 (3)	29 (4)	0 (0)
Inflammatory bowel disease****	32 (3)	29 (4)	3 (1)
Chronic liver disease††††	14 (1)	14 (2)	0 (0)

* Overall, 6% of patients had missing data for anemia, 1% for obesity and alcohol abuse, and < 1% for metastatic cancer.
† ≥2 items on modified Charlson Comorbidity Index.
‡ Treated or untreated.
§ Hemoglobin < 13 g/dL in men or < 12 g/dL in women.
¶ Body mass index ≥30 kg/m^2.
** Chronic renal disease (i.e. chronic renal failure with or without hemodialysis) such as diabetic or hypertensive nephropathy, chronic glomerulonephritis, chronic interstitial nephritis, myeloma-related nephropathy, or cystic kidney disease.
†† Leukemia, lymphoma, or non-metastatic solid cancer requiring chemotherapy, radiotherapy, surgery, or palliative care during the last three months, excluding local skin tumors such as basal cell carcinoma and spinal cell carcinoma.
‡‡ Stable or unstable angina pectoris, prior myocardial infarction (ST or non ST elevation), prior coronary angioplasty or known significant stenosis (i.e. > 50%), or prior coronary bypass surgery.
§§ Treated or untreated.
¶¶ Any known chronic lung disease such as chronic obstructive pulmonary disease, active asthma, lung fibrosis, cystic fibrosis, or bronchiectasis.
*** Systolic or diastolic heart failure, left or right heart failure, forward or backward heart failure, or left ventricular ejection fraction < 40%, and/or an episode of acute heart failure NYHA III or IV during last three months.
††† Defined as consumption of > 14 units/week in men or > 7 units/week in women [55].
‡‡‡ History of ischemic or hemorrhagic stroke, or transient ischemic attack.
§§§ Acute lumbar pain or sciatica or vertebral compression, acute arthritis of the legs, or an acute episode of rheumatoid arthritis in the legs during the last three months.
¶¶¶ Including hemiparesis.
**** Known history of Crohn's disease, or ulcerative colitis.
†††† Liver cirrhosis, chronic hepatitis, chronic liver failure, or hemochromatosis.

2.4. Study outcomes

The primary outcomes were adverse clinical events, i.e. fatal and non-fatal recurrent VTE and major bleeding, and all-cause mortality. VTE recurrence was defined as a new or recurrent, symptomatic, and objectively confirmed DVT and/or PE during follow-up, in accordance with previously described imaging criteria [28,29]. Major bleeding was defined as a fatal bleeding, bleeding in a critical location (intracranial,

intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, or intramuscular with compartment syndrome), a bleeding with reduction of hemoglobin ≥20 g/l, or a bleeding leading to the transfusion of ≥2 units of packed red blood cells [30]. Our secondary outcome was the quality of anticoagulation therapy measured as the percentage of time spent in the therapeutic INR range (2.0–3.0).

During follow-up, patients were contacted semi-annually, alternating between face-to-face evaluations and telephone calls. Detailed information regarding the date and type and circumstance of outcomes were collected from the patient, and/or the patient's family members, primary care physician, and the medical chart. All outcomes were reviewed and adjudicated by a committee of three blinded clinical experts. Based on the full consensus of this committee, deaths were classified as definitely due to PE (e.g., confirmed by autopsy or following severe PE), possibly due to PE (e.g., sudden death without obvious cause), due to major bleeding and due to other causes. Bleeding-related death was defined as death following intracranial hemorrhage or hemodynamic deterioration due to major bleeding [31]. In patients treated with vitamin K antagonists, we also collected all INR values. In Switzerland, vitamin K antagonist treatment is usually monitored by family physicians.

2.5. Statistical analyses

We compared differences in patient baseline characteristics between multimorbid and non-multimorbid patients using the chi-squared test. We used Kaplan-Meier estimates and log-rank tests to compare the cumulative incidence of VTE recurrence, major bleeding, and all-cause mortality between multimorbid and non-multimorbid patients. We examined the association between comorbid burden and recurrent VTE and major bleeding using competing risk regression models according to Fine and Gray [32], accounting for death as a competing event. The strength of the association between comorbid burden and the risk of recurrent VTE and major bleeding was reflected by the sub-hazard ratio (SHR), which is the ratio of hazards associated with the cumulative incidence function in the presence and absence of comorbid burden. Comorbid burden was introduced as a dichotomous (multimorbid vs. non-multimorbid) and as a continuous variable (mCCI score) into the models. Patients who withdrew their consent or were lost to follow-up were censored at the time of the last contact. In a first analysis, we adjusted for patient demographics (age, sex) and periods of anticoagulation as a time-varying covariate to minimize the risk of confounding by treatment, as the durations of anticoagulation may have differed by localization and type of VTE. In the final model, we also adjusted for risk factors that have been previously shown to be associated with recurrent VTE (history of VTE, localization [PE ± DVT vs. DVT only], and type of index VTE [provoked vs. unprovoked]) [33–37] and bleeding (history of bleeding, recent surgery, risk of falls, physical activity level, thrombocytopenia, concomitant antiplatelet/NSAID therapy) [38–43]. We performed a single imputation procedure assuming missing values to be normal.

We calculated the mean percentage of time spent within (2.0–3.0), above (> 3.0), and below (< 2.0) the therapeutic INR range according to Rosendaal's method [44], excluding the first seven days of treatment. We compared the time spent in a given INR range by multimorbidity and the mCCI score using the unpaired *t*-test for means and analysis of variance (ANOVA), respectively. Statistical analyses were done using Stata 14. A two-sided *P*-value < 0.05 was considered statistically significant.

3. Results

3.1. Study sample

Of 1863 screened patients ≥ 65 years of age with acute VTE, we excluded 462 patients who had at least one exclusion criterion and 398 who did not consent to participate (Fig. 1). After the additional exclusion of 12 patients who withdrew informed consent very early or refused the use of their data, our final study sample comprised 991 patients. Excluded patients were significantly older (median age, 78 vs. 75 years; $P < 0.001$) and more likely to be women (59% vs. 47%; $P < 0.001$) than analyzed patients.

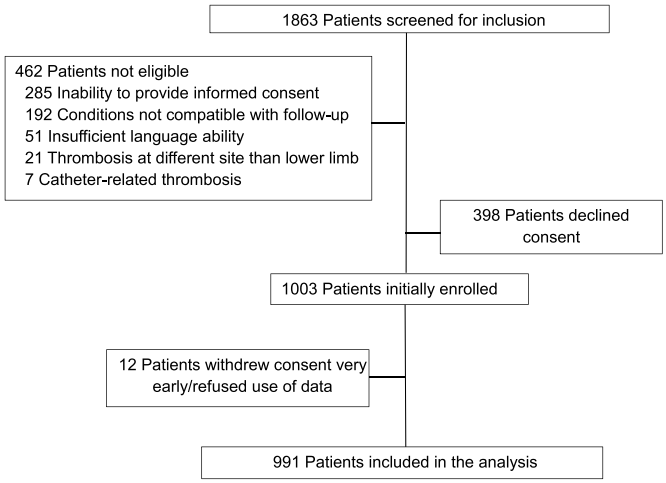

Fig. 1. Patient flow chart.

Overall, 708 (71%) patients were multimorbid, most of whom presented two or three concurrent comorbidities (Fig. 2). The overall mean mCCI score (standard deviation) was 2.7 (1.8) points. Arterial hypertension, anemia, and obesity were the most common comorbid conditions (Table 1). Active cancer was reported in 178 (18%) patients, with 72 (7%) presenting metastatic cancer (Table 1).

Multimorbid patients were older and more likely to have a history of bleeding, a high risk of falls, a low physical activity level, cancer-related VTE, and concomitant treatment with platelet inhibitors or nonsteroidal anti-inflammatory drugs (Table 2). Multimorbid patients were also more likely to receive unfractionated heparin and less likely to receive vitamin K antagonist treatment and to be managed in the outpatient setting.

3.2. Clinical outcomes

The mean follow-up period was 28 (standard deviation 13) months. During follow-up, 122 (12%) patients experienced recurrent VTE and 132 (13%) had major bleeding. Overall, 206 (21%) patients died. Of

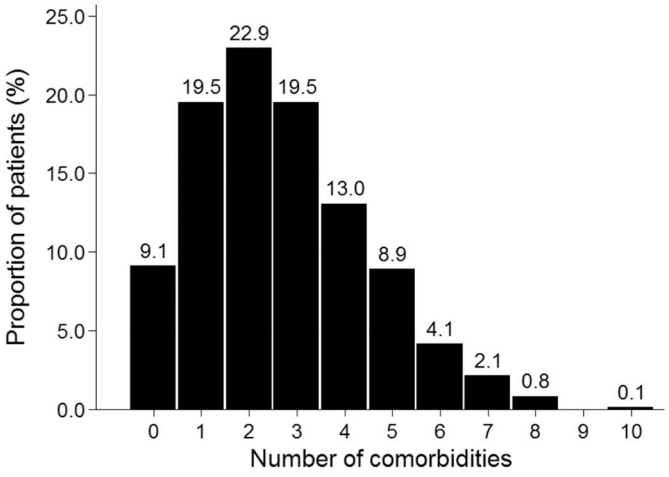

Fig. 2. Distribution of comorbidities based on the modified Charlson Comorbidity Index (mCCI).

Table 2
Patient baseline characteristics by multimorbidity status.

Characteristic*	Multimorbid† (*N* = 708)	Non-multimorbid (*N* = 283)	*P*-value
	n (%) or mean (SD)		
Age categories - years			0.004
65–69	164 (23)	87 (31)	
70–74	156 (22)	74 (26)	
75–79	154 (22)	57 (20)	
≥ 80	234 (33)	65 (23)	
Female sex	333 (47)	130 (46)	0.778
History of VTE	195 (28)	88 (31)	0.276
History of bleeding	85 (12)	16 (6)	0.002
Recent surgery	119 (17)	30 (11)	0.014
High risk of falls‡	355 (50)	102 (36)	< 0.001
Low physical activity level§	301 (43)	66 (23)	< 0.001
Polypharmacy¶	434 (61)	70 (25)	< 0.001
Platelet count < 150 G/l	109 (16)	31 (13)	0.214
Location of index VTE			0.446
PE ± DVT	496 (70)	191 (67)	
DVT only	212 (30)	92 (33)	
Precise location of index VTE			0.302
Proximal DVT only	143 (20)	54 (19)	
Distal DVT only	81 (11)	27 (10)	
Proximal and distal DVT	87 (12)	47 (17)	
PE only	397 (56)	155 (55)	
Type of index VTE			< 0.001
Provoked**	152 (21)	63 (22)	
Unprovoked††	384 (54)	214 (76)	
Cancer-related‡‡	172 (24)	6 (2)	
Treatments			
Concomitant antiplatelet/ NSAID therapy	319 (45)	61 (22)	< 0.001
Initial parenteral anticoagulant			< 0.001
Low-molecular weight heparin	327 (46)	138 (49)	
Unfractionated heparin	264 (37)	69 (24)	
Fondaparinux	91 (13)	67 (24)	
Danaparoid	1 (< 1)	0 (< 1)	
No parenteral anticoagulation	25 (4)	9 (3)	
Subsequent VKA therapy	588 (83)	273 (96)	< 0.001
Thrombolysis	18 (3)	12 (4)	0.157
Thrombembolectomy	1 (< 1)	2 (1)	0.198
Inferior vena cava filter	7 (1)	4 (1)	0.520
Outpatient care	112 (16)	74 (26)	< 0.001

Abbreviations: SD, standard deviation; VTE, venous thromboembolism; PE, pulmonary embolism; DVT, deep vein thrombosis; NSAID, non-steroidal anti-inflammatory drug; VKA, vitamin K antagonist.

* Data for platelet count were missing in 6% of patients.

† ≥2 items on modified Charlson Comorbidity Index.

‡ Self-reported fall during the last year or problems with gait, balance, or mobility.

§ Mostly lying/sitting activity or avoidance to climb stairs/carry light weight.

¶ Prescription of > 4 drugs, including St. John's wort, at the time of the index VTE event.

** Major surgery, estrogen therapy, or immobilization (bed rest > 72 h, fracture or cast of the lower extremity, voyage in sitting position > 6 h) during the last three months before the index VTE.

†† Absence of major surgery, estrogen therapy, immobilization, or active cancer during the last three months before the index VTE.

‡‡ Leukemia, lymphoma, or metastatic or non-metastatic solid cancer requiring surgery, chemotherapy, radiotherapy, or palliative care during the last three months before the index VTE, excluding local skin tumors such as basal cell carcinoma and spinal cell carcinoma.

these, 36 (17%) died from PE and 13 (6%) from bleeding. Multimorbid patients were significantly more likely to die from PE than non-multimorbid patients (5% vs. 1%; $P = 0.001$), while bleeding-related mortality did not differ significantly (2% vs. < 1%; $P = 0.124$). Although the 3-year cumulative incidence of recurrent VTE was higher in multimorbid than in non-multimorbid patients, the difference did not reach statistical significance (Fig. 3, panel A). The incidence rate of recurrent VTE was 6.5 (95% confidence interval [CI] 5.3 to 8.0) per 100 patient-years in multimorbid vs. 4.0 (95% CI 2.8 to 5.8) per 100 patient-years in non-multimorbid patients. The cumulative incidence of major bleeding and all-cause mortality was significantly higher in

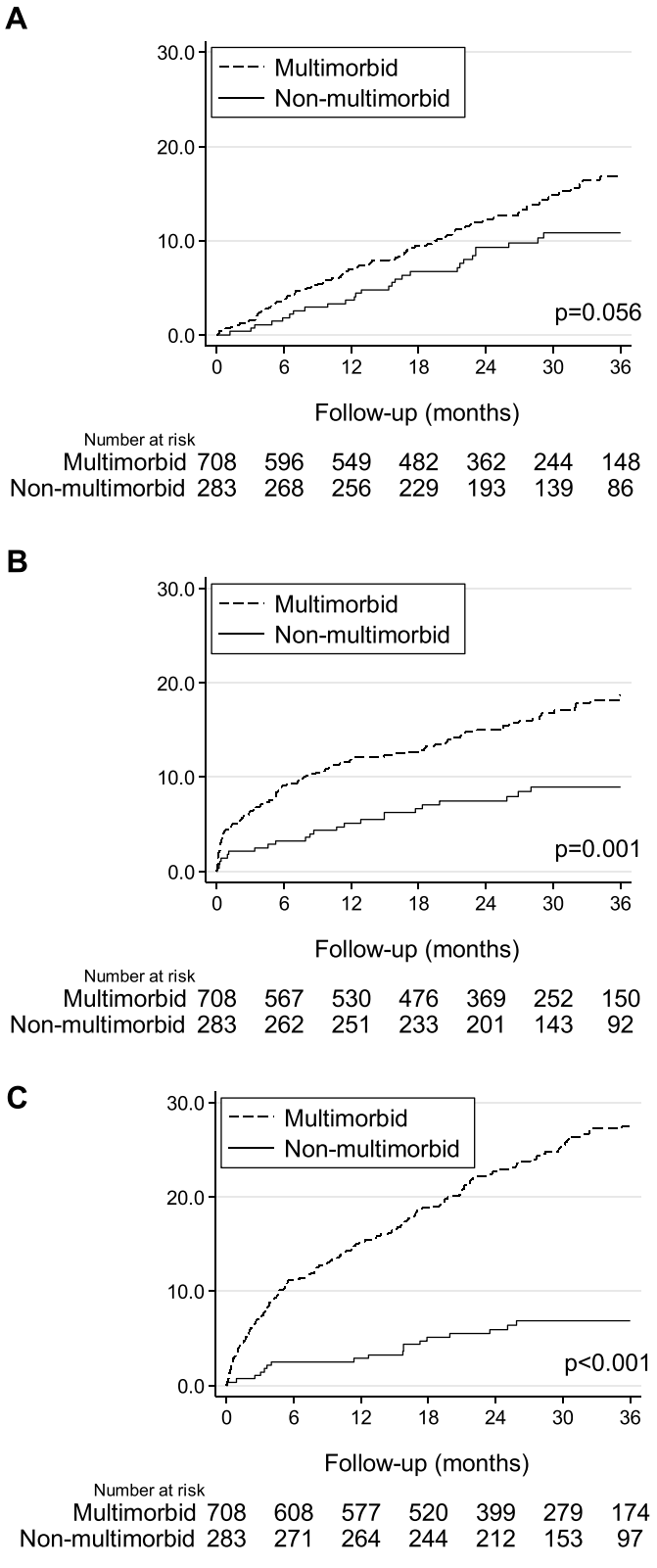

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Fig. 3. Panel A. Kaplan-Meier estimates of first recurrent venous thromboembolic event by multimorbidity
The 3-year cumulative incidence of a first recurrent venous thromboembolic event was 16.8% for multimorbid and 10.8% for non-multimorbid patients ($P = 0.056$ by the log-rank test).
Panel B. Kaplan-Meier estimates of a first major bleeding event by multimorbidity
The 3-year cumulative incidence of a first major bleeding event was 18.7% in multimorbid and 9.0% in non-multimorbid patients ($P = 0.001$ by the log-rank test).
Panel C. Kaplan-Meier estimates of overall mortality by multimorbidity
The 3-year cumulative incidence of death was 27.5% for multimorbid and 6.9% for non-multimorbid patients ($P < 0.001$ by the log-rank test).

multimorbid patients (Fig. 3, panels B and C). The incidence rates for major bleeding and all-cause mortality were 7.7 (95% CI 6.4 to 9.3) and 12.0 (95% CI 10.4 to 13.8) per 100 patient-years in multimorbid vs. 3.3 (95% CI 2.2. to 4.9) and 2.9 (95% CI 1.9 to 4.4) per 100 patient-years in non-multimorbid patients.

3.3. Association between multimorbidity and clinical outcomes

After adjustment for patient demographics and periods of anticoagulation, multimorbidity was significantly associated with recurrent VTE (SHR 1.61, 95% CI 1.04–2.48) and major bleeding (SHR 1.94, 95% CI 1.23–3.05) (Table 3). After additional adjustment for known risk factors for recurrent VTE, the association between multimorbidity and VTE recurrence remained significant (SHR 1.66, 95% CI 1.08–2.57). Although multimorbid patients had a higher risk of major bleeding than non-multimorbid patients (SHR 1.55, 95% CI 0.96–2.50), the association failed to achieve statistical significance in the final model by a small margin (Table 3). The number of comorbid conditions based on the mCCI was not statistically significantly associated with recurrent VTE or major bleeding in the final model.

3.4. Multimorbidity and anticoagulation quality

We assessed the quality of oral anticoagulation in the 821 of 991 (83%) patients who received vitamin K antagonists and for whom INR values could be obtained. Multimorbid patients spent significantly less time in the therapeutic (2.0–3.0) and significantly more time in the supratherapeutic INR range (> 3.0) than non-multimorbid patients (Table 4). Patients with higher mCCI scores spent less time in the therapeutic INR range. Patients with a mCCI score ≥ 4 spent the least time in the therapeutic INR range and were more likely to be over- as well as underanticoagulated.

4. Discussion

Our results demonstrate that over 70% of elderly patients with acute VTE are multimorbid and that such patients not only have a lower anticoagulation quality but also a higher incidence of adverse clinical events. After adjustment, multimorbid patients had a statistically significantly higher risk of recurrent VTE and a higher risk of major bleeding, although the latter failed to achieve statistical significance by a small margin. Multimorbid patients were also more likely to die from PE.

To our knowledge, our study is the first work that specifically examined the quality of anticoagulation in multimorbid patients with acute VTE and whether comorbid burden was associated with recurrent VTE and major bleeding. Our findings are consistent with prior studies demonstrating that a greater comorbid burden was associated with a lower anticoagulation quality in patients with atrial fibrillation and other indications for anticoagulation [7,8,45,46]. In an older retrospective cohort study enrolling anticoagulated patients (30% of whom had VTE), the presence of ≥3 comorbid conditions was associated with serious bleeding (relative risk 1.4) [9].

In our study, patients with a higher number of comorbid conditions spent less time in the therapeutic range and were more likely to be over- and underanticoagulated. The relationship between multimorbidity, anticoagulation quality, and thromboembolic/bleeding-related complications is complex. Multimorbidity is strongly associated with polypharmacy and use of platelet inhibitors, leading to drug interactions, less stable INR levels, and bleedings [17,27,47,48]. Patients with polypharmacy may also have a greater risk of falls and fall-related bleeds [49], resulting from drug-induced oversedation and orthostatic hypotension [50,51]. Moreover, several comorbid conditions are recognized risk factors for recurrent VTE (e.g., inflammatory bowel

Table 3
Association between multimorbidity, cumulative number of comorbidities, and clinical outcomes.

Clinical outcome	Crude SHR (95% CI)	*P*-value	Age- and sex-adjusted* SHR (95% CI)	*P*-value	Fully adjusted† SHR (95% CI)	*P*-value
Recurrent VTE						
Non-multimorbid	Reference	–	Reference	–	Reference	–
Multimorbid	1.40 (0.92–2.14)	0.116	1.61 (1.04–2.48)	0.031	1.66 (1.08–2.57)	0.021
Per 1 mCCI point	1.03 (0.94–1.13)	0.519	1.06 (0.97–1.16)	0.209	1.08 (0.98–1.19)	0.101

Clinical outcome	Crude SHR (95% CI)	*P*-value	Age- and sex-adjusted* SHR (95% CI)	*P*-value	Fully adjusted‡ SHR (95% CI)	*P*-value
Major bleeding						
Non-multimorbid	Reference	–	Reference	–	Reference	–
Multimorbid	2.01 (1.29–3.15)	0.002	1.94 (1.23–3.05)	0.004	1.55 (0.96–2.50)	0.076
Per 1 mCCI point	1.14 (1.05–1.23)	0.001	1.13 (1.04–1.23)	0.003	1.05 (0.95–1.15)	0.350

Abbreviations: SHR, sub-hazard ratio; CI, confidence interval; VTE, venous thromboembolism; mCCI, modified Charlson Comorbidity Index.
* Adjusted for age, sex, and periods of anticoagulation as a time-varying covariate.
† Adjusted for age, sex, history of VTE, localization and type of index VTE, and periods of anticoagulation as a time-varying covariate.
‡ Adjusted for age, sex, history of bleeding, recent surgery, risk of falls, physical activity level, thrombocytopenia, concomitant antiplatelet/NSAID therapy, and periods of anticoagulation as a time-varying covariate.

Table 4
Mean percentage of time in a given INR range.

	INR 2.0–3.0			INR > 3.0			INR < 2.0		
	Mean % (SD)		*P*-value	Mean % (SD)		*P*-value	Mean % (SD)		*P*-value
Multimorbidity*			0.009			0.027			0.321
No	65	(22)		13	(16)		22	(21)	
Yes	61	(23)		16	(18)		23	(21)	
mCCI score			< 0.001			0.068			0.004
0–1	65	(22)		13	(16)		22	(21)	
2	66	(23)		15	(19)		19	(20)	
3	61	(23)		15	(16)		24	(22)	
≥ 4	56	(21)		17	(17)		27	(21)	

Abbreviations: INR, International normalized ratio; SD, standard deviation; mCCI, modified Charlson Comorbidity Index.
* ≥2 items on modified Charlson Comorbidity Index.

disease, obesity) [20–23], anticoagulation-related bleeding (e.g., chronic renal and liver disease, arterial hypertension) [24,38,52], or both (e.g., active cancer) [53]. While the nature and full extent of possible drug-drug, drug-disease, and disease-disease interactions are incompletely understood in multimorbid patients receiving vitamin K antagonists (VKAs) for VTE, the net effect is a poor anticoagulation quality and a higher risk of complications.

Our findings have several clinical and research implications. First, given their lower anticoagulation quality and higher risk of complications, multimorbid elderly patients could benefit from a more intensive clinical and anticoagulation surveillance. Direct oral anticoagulants have a much lower drug interaction potential, provide a more stable anticoagulation effect, and have a slightly lower risk of major bleeding than VKAs [54]. However, whether a switch from VKAs to direct oral anticoagulants in multimorbid patients without severe renal failure would be beneficial, is currently unknown. Second, evidence suggests that multimorbid elderly patients are underrepresented in clinical anticoagulation trials because such patients are often excluded from trial participation [14]. A new generation of pragmatic anticoagulation trials is needed that explicitly enroll patients with comorbidities, risk factors for thrombosis and bleeding, and suboptimal therapeutic adherence. Novel VTE recurrence and bleeding risk assessment tools applicable to elderly multimorbid patients should also be developed to allow for a better risk stratification of such high-risk patients.

Our study has potential limitations. First, as our study excluded patients with a limited life expectancy and those with severe dementia, analyzed patients were younger than excluded patients and therefore may not represent the sickest patients with VTE. We suspect that the inclusion of such patients would have made the association between multimorbidity and adverse outcomes even stronger. Furthermore, as we included only patients aged ≥65 years, our findings cannot be extrapolated to younger populations. Second, because there is no commonly accepted method to conceptualize multimorbidity in patients with VTE (or any other disease) [3,16], the greatest challenge of our study was to find a clinically credible concept for multimorbidity. We chose to adapt the Charlson Comorbidity Index by adding several variables (anemia, alcohol abuse, inflammatory bowel disease, obesity, and arterial hypertension) that are commonly used in comorbidity assessments [19], and are known to be associated with VTE recurrence [20–23], bleeding [24,25], or anticoagulation quality [26,27]. Although we captured a large number of relevant comorbid conditions, we could not assess the severity of these diseases. Moreover, other comorbid conditions that were not available in our database (e.g., psychiatric diseases) could potentially influence anticoagulation quality and outcomes in patients with VTE [27]. As the mCCI is a first attempt to conceptualize multimorbidity in patients with VTE, it lacks external validation. We believe that a consensus-based core set of comorbid conditions with impact on VTE-related treatments and complications should be established and validated for future use in randomized and non-randomized anticoagulation trials. Finally, although we adjusted for periods of anticoagulation, we cannot entirely exclude that possibility that outcome differences between multimorbid vs. non-multimorbid patients were due to differing types and quality of anticoagulation.

In conclusion, our findings demonstrate that the majority of elderly patients with acute VTE are multimorbid. Patients with a higher comorbid burden have a lower quality of anticoagulation and a higher complication rate. Novel risk stratification tools and pragmatic anticoagulation trials with explicit enrolment of multimorbid patients are needed to determine the optimal duration of anticoagulation in multimorbid persons with VTE.

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Addendum

N. Lange, O. Stalder, A. Limacher, and D. Aujesky were responsible for study design and statistical analyses. N. Lange and D. Aujesky wrote the manuscript. O. Stalder, A. Limacher, M. Méan, T. Tritschler and N. Rodondi critically reviewed the manuscript. N. Rodondi and D. Aujesky collected data and obtained funding from the Swiss National Science Foundation.

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Conflict of interest

The authors declare that they have no conflict of interest.

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