Polypharmacy is Associated with an Increased Risk of Bleeding in Elderly Patients with Venous Thromboembolism

Waltraud Leiss, MD[1], Marie Méan, MD[1], Andreas Limacher, PhD, MAS, MSc[2], Marc Righini, MD[3], Kurt Jaeger, MD[4], Hans-Jürg Beer, MD[5], Joseph Osterwalder, MD, MPH[6], Beat Frauchiger, MD[7], Christian M. Matter, MD[8], Nils Kucher, MD[9], Anne Angelillo-Scherrer, MD[10], Jacques Cornuz, MD, MPH[11], Martin Banyai, MD[12], Bernhard Lämmle, MD[10], Marc Husmann, MD[13], Michael Egloff, MD[5], Markus Aschwanden, MD[4], Nicolas Rodondi, MD, MAS[1], and Drahomir Aujesky, MD, MSc[1]

[1]Department of General Internal Medicine, Bern University Hospital, Bern, Switzerland; [2]Clinical Trials Unit Bern, Department of Clinical Research, and Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland; [3]Division of Angiology and Hemostasis, Geneva University Hospital, Geneva, Switzerland; [4]Division of Angiology, Basel University Hospital, Basel, Switzerland; [5]Cantonal Hospital of Baden, Baden, Switzerland; [6]Emergency Department, Cantonal Hospital of St. Gallen, St. Gallen, Switzerland; [7]Department of Internal Medicine, Cantonal Hospital of Frauenfeld, Frauenfeld, Switzerland; [8]Cardiovascular Research, Institute of Physiology, Zurich Center for Integrative Human Physiology, University of Zurich, and Division of Cardiology, Zurich University Hospital, Zurich, Switzerland; [9]Division of Angiology, Bern University Hospital, Bern, Switzerland; [10]Department of Hematology and Central Hematology Laboratory, Bern University Hospital, Bern, Switzerland; [11]Department of Ambulatory Care and Community Medicine, University of Lausanne, Lausanne, Switzerland; [12]Division of Angiology, Cantonal Hospital of Lucerne, Lucerne, Switzerland; [13]Division of Angiology, Zurich University Hospital and University of Zurich, Zurich, Switzerland.

BACKGROUND: Polypharmacy, defined as the concomitant use of multiple medications, is very common in the elderly and may trigger drug-drug interactions and increase the risk of falls in patients receiving vitamin K antagonists.

OBJECTIVE: To examine whether polypharmacy increases the risk of bleeding in elderly patients who receive vitamin K antagonists for acute venous thromboembolism (VTE).

DESIGN: We used a prospective cohort study.

PARTICIPANTS: In a multicenter Swiss cohort, we studied 830 patients aged ≥ 65 years with VTE.

MAIN MEASURES: We defined polypharmacy as the prescription of more than four different drugs. We assessed the association between polypharmacy and the time to a first major and clinically relevant non-major bleeding, accounting for the competing risk of death. We adjusted for known bleeding risk factors (age, gender, pulmonary embolism, active cancer, arterial hypertension, cardiac disease, cerebrovascular disease, chronic liver and renal disease, diabetes mellitus, history of major bleeding, recent surgery, anemia, thrombocytopenia) and periods of vitamin K antagonist treatment as a time-varying covariate.

KEY RESULTS: Overall, 413 (49.8 %) patients had polypharmacy. The mean follow-up duration was 17.8 months. Patients with polypharmacy had a significantly higher incidence of major (9.0 vs. 4.1 events/100 patient-years; incidence rate ratio [IRR] 2.18, 95 % confidence interval [CI] 1.32–3.68) and clinically relevant non-major bleeding (14.8 vs. 8.0 events/100 patient-years; IRR 1.85, 95 % CI 1.27–2.71) than patients without polypharmacy. After adjustment, polypharmacy was significantly associated with major (sub-hazard ratio [SHR] 1.83, 95 % CI 1.03–3.25) and clinically relevant non-major bleeding (SHR 1.60, 95 % CI 1.06–2.42).

CONCLUSIONS: Polypharmacy is associated with an increased risk of both major and clinically relevant non-major bleeding in elderly patients receiving vitamin K antagonists for VTE.

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INTRODUCTION

Polypharmacy, defined as the concomitant use of multiple medications, is very common in elderly.[1] Overall, between 13 % and 39 % of persons aged 65 years or older receive treatment with more than four drugs.[1–3] Prior evidence, based essentially on patients with atrial fibrillation, suggests that polypharmacy may increase the risk of bleeding in patients treated with vitamin K antagonists.[4–9] Several reasons could explain why polypharmacy is associated with bleeding. First, various drugs, such as amiodarone and erythromycin, alter pharmacokinetics and pharmacodynamics of vitamin K antagonists and may potentiate their anticoagulant effect.[10] Second, several medication classes, such as sedatives and antihypertensive medications, may increase the risk of fall-related

bleeding.[11] Third, the combination of platelet inhibitors and oral anticoagulants may further increase the bleeding risk.[12] Finally, polypharmacy could be an indicator of disease burden, which may in itself contribute to a higher risk of bleeding.[13]

Acute venous thromboembolism (VTE) is common in elderly persons, with an incidence between 2.8 and 4.1 cases per 1,000 person-years in persons aged ≥ 65 years.[14] Recurrent VTE is effectively prevented with vitamin K antagonist treatment for three months or longer. However, the risk of anticoagulation-related major bleeding is substantial, with an incidence rising up to 5 % per year in patients aged 75 years and older.[15] Although elderly patients with VTE are typically multimorbid and may receive multiple drug treatments,[16] to our knowledge, the relationship between polypharmacy and the risk of bleeding has never been examined in this high-risk population. In a prospective, multicenter cohort of elderly patients receiving vitamin K antagonists for VTE, we sought to examine the association between polypharmacy and risk of bleeding, adjusting for multiple known bleeding risk factors.

MATERIALS AND METHODS

Cohort Sample

The study was conducted between September 2009 and September 2012 as part of an ongoing prospective, multicenter cohort study to assess long-term medical outcomes in 1,003 consecutive inpatients and outpatients aged ≥ 65 years with acute, symptomatic VTE from all five Swiss university hospitals and four high-volume non-university hospitals. A full description of the cohort methods, including eligibility criteria, definition of VTE, and follow-up procedures, has been published elsewhere.[17,18] Anticoagulant treatment (i.e., parenteral anticoagulant followed by vitamin K antagonists or parenteral anticoagulation alone) was left to the discretion of the managing hospital and primary care physicians. For this project, we excluded all patients who did not receive oral anticoagulation with vitamin K antagonists within 14 days of the index VTE event.

Baseline Data Collection

For all enrolled patients, trained study nurses prospectively collected information about baseline demographics (age, gender), comorbid conditions (active cancer, arterial hypertension, cardiac disease, cerebrovascular disease, chronic liver disease, chronic renal disease, diabetes mellitus, history of major bleeding, recent surgery), laboratory findings (hemoglobin, platelet count), VTE-related treatment (oral and parenteral anticoagulants, thrombolysis, insertion of an inferior vena cava filter), type and localization of index VTE event, and concomitant antiplatelet/non-steroidal anti-inflammatory drug therapy using standardized data collection forms. We assessed the risk of falls using two validated screening questions:[19] 1) Did you fall during the last year? If not, then 2) Did you notice any problem with gait, balance, or mobility? Patients who answered yes to at least one screening question were considered to be at high risk of falls. We also recorded all available international normalized ratio (INR) measurements at baseline and during follow-up using inpatient laboratory data and the patients' personal anticoagulation monitoring cards.

Definition of Polypharmacy

We also recorded the presence of polypharmacy at the time of study enrollment, defined as the prescription of more than four drugs, including St. John's wort, at the time of the index VTE event.[4] The intake of vitamins or alternative medicine treatments was not considered.

Study Outcomes

Our primary outcome was the time to a first major bleeding during follow-up. We defined major bleeding as fatal bleeding, symptomatic bleeding at critical sites (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome), or clinically overt bleeding with a reduction of haemoglobin of at least 20 g/L, or leading to transfusion of two or more units of packed red blood cells.[20] The secondary outcome was the time to a clinically relevant non-major bleeding, defined as a bleeding event that required medical attention (a physician consultation or a visit at the emergency department), but that did not meet the criteria for major bleeding.

Follow-up included one telephone interview and two face-to-face evaluations during the first year of study participation, and then semi-annual contacts, alternating between face-to-face evaluations (clinic visits or home visits in housebound patients) and telephone calls. During each visit/contact, study nurses interviewed patients to obtain information about the date and type of bleeding events and if the bleeding was fall-related. If a clinical event occurred, information was complemented by reviewing medical charts and interviewing patients' primary care physicians and/or family members.

A committee of three independent blinded clinical experts reviewed and adjudicated all outcome events. Death was considered to be bleeding-related if it followed an intracranial hemorrhage or a bleeding episode leading to hemodynamic deterioration. All other deaths were classified as not bleeding-related.[21] Final classification was based on the full consensus of this committee.

Statistical Analyses

We compared baseline characteristics of patients with and without polypharmacy using Fisher's exact test for categorical variables and the non-parametric Wilcoxon rank-sum test for

continuous variables. We calculated the overall incidence rates of major and clinically relevant non-major bleeding in patients with and without polypharmacy and compared the cumulative incidence of bleedings using the Kaplan-Meier technique and the logrank test. We also compared the percent of time spent in a given INR range (<2.0, 2.0–3.0, >3.0) by the unpaired t-test,[22] excluding all international normalized ratio (INR) values measured during the first seven days of vitamin K antagonist treatment.

Because elderly multimorbid patients are at competing risk of dying from non-hemorrhagic causes before experiencing bleeding, we examined the associations between polypharmacy and the time of a first major and clinically relevant non-major bleeding using competing risk regression analysis, accounting for death as a competing event.[23] We accounted for non-hemorrhagic death as a competing event when analyzing major bleeding and overall death when analyzing clinically relevant non-major bleeding. The strength of the association between polypharmacy and bleeding is reflected by the sub-hazard ratio (SHR), which is the ratio of hazards associated with the cumulative incidence function in the presence of a competing risk. We adjusted for risk factors that had been previously shown to be associated with major bleeding, including age, female gender, pulmonary embolism at baseline, active cancer, arterial hypertension, cardiac disease, cerebrovascular disease, chronic liver and renal disease, diabetes mellitus, history of major bleeding, recent surgery, anemia, thrombocytopenia, and the periods of vitamin K antagonist treatment as a time-varying covariate.[24–29] Because the use of antiplatelet/non-steroidal anti-inflammatory therapy was included in our definition of polypharmacy, we did not adjust for this variable in our primary analysis. However, given the known association between the use of antiplatelet/non-steroidal anti-inflammatory drugs and the risk of bleeding in patients receiving vitamin K antagonists,[12,30] the models were also adjusted for this variable in a secondary analysis. Moreover, to explore the potential effect of falls on the association between polypharmacy and anticoagulation-related

Table 1. Baseline Characteristics

	All (n=830)	Polypharmacy (n=413)	No polypharmacy (n=417)	*p* value
Characteristics[a]	n (%) or median (range)			
Age, years	75 (65–97)	77 (65–96)	74 (65–97)	< 0.001
Female gender	390 (47.0)	198 (47.9)	192 (46.0)	0.63
Overt pulmonary embolism	599 (72.2)	307 (74.3)	292 (70.0)	0.19
Active cancer[b]	71 (8.6)	49 (11.9)	22 (5.3)	< 0.001
Arterial hypertension	542 (65.3)	321 (77.7)	221 (53.0)	< 0.001
Cardiac disease[c]	199 (24)	146 (35.4)	53 (12.7)	< 0.001
Cerebrovascular disease[d]	73 (8.8)	55 (13.3)	18 (4.3)	< 0.001
Chronic liver disease[e]	12 (1.4)	6 (1.5)	6 (1.4)	1.00
Chronic renal disease[f]	153 (18.4)	100 (24.2)	53 (12.7)	< 0.001
Diabetes mellitus	131 (15.8)	97 (23.5)	34 (8.2)	< 0.001
History of major bleeding[g]	75 (9.0)	52 (12.6)	23 (5.5)	< 0.001
Recent surgery[h]	115 (13.9)	72 (17.4)	43 (10.3)	0.003
High risk of falls[i]	377 (45.4)	239 (57.9)	138 (33.1)	< 0.001
Anemia[j]	281 (33.9)	185 (44.8)	96 (23.0)	< 0.001
Thrombocytopenia[k]	114 (13.7)	65 (15.7)	49 (11.8)	0.19
Antiplatelet/NSAID therapy[l]	330 (39.8)	238 (57.6)	92 (22.1)	< 0.001
Pre-existing VKA treatment	44 (5.3)	31 (7.5)	13 (3.1)	0.005
Initial parenteral anticoagulation				0.009
Low-molecular-weight heparin	386 (46.5)	184 (44.6)	202 (48.4)	
Dalteparin	69 (17.8)	29 (15.7)	40 (19.8)	
Enoxaparin	164 (42.4)	92 (49.7)	72 (35.6)	
Nadroparin	153 (39.5)	63 (34.05)	90 (44.55)	
Unfractionated heparin	278 (33.5)	159 (38.5)	119 (28.5)	
Fondaparinux	143 (17.2)	58 (14.0)	85 (20.4)	
Danaparoid	1 (0.1)	1 (0.2)		
No parenteral anticoagulation	22 (2.7)	11 (2.7)	11 (2.6)	
Inferior vena cava filter	5 (0.6)	2 (0.5)	3 (0.7)	1.00
Thrombolysis	24 (2.9)	5 (1.2)	19 (4.6)	0.006

Abbreviations: NSAIDnon-steroidal anti-inflammatory drug; VKAvitamin K antagonist
[a]Values were missing for history of major bleeding (0.1 %), thrombocytopenia (7.0 %), and anemia (7.0 %)
[b]Solid or hematologic cancer requiring chemotherapy, radiation therapy, surgery, or palliative care during the last three months
[c]Systolic or diastolic heart failure, left or right heart failure, forward or backward heart failure, left ventricular ejection fraction of < 40 %, acute heart failure, or a myocardial infarction with or without ST elevation during the last three months, or history of coronary heart disease
[d]History of ischemic or hemorrhagic stroke or a transient ischemic attack
[e]Liver cirrhosis, chronic hepatitis, chronic liver failure, or hemochromatosis
[f]Diabetic or hypertensive nephropathy, chronic glomerulonephritis, chronic interstitial nephritis, myeloma-related nephropathy, or cystic kidney disease
[g]Bleeding that led to a hospital stay or transfusions
[h]Surgery requiring general or spinal anesthesia during the last three months
[i]Self-reported fall during the last year or any problem with gait, balance, or mobility
[j]Hemoglobin < 13 g/dL for men and < 12 g/dL for women
[k]Platelet count <150,000/μL
[l]Use of any antiplatelet therapy, such as aspirin, clopidogrel, prasugrel, aspirin/dipyridamol, or use of non-steroidal anti-inflammatory drugs

bleeding, we additionally adjusted for the risk of falls in another secondary analysis. While missing values at baseline were generally assumed to be normal, we assumed missing values to be abnormal in a sensitivity analysis. A two-sided p value < 0.05 was considered statistically significant. All analyses were done using Stata 12 (Stata Corporation, College Station, Texas).

RESULTS

Study Sample

Of 1,003 patients enrolled in the cohort, we excluded ten patients who withdrew consent within one day from inclusion or who withdrew consent during follow-up and did not allow use of data. After the exclusion of 163 patients who did not receive vitamin K antagonists during the first 14 days of VTE diagnosis, our final study sample comprised 830 patients. The 163 excluded patients who did not receive vitamin K antagonists did not differ in age and gender, but were statistically significantly more likely to have active cancer than the 830 analyzed patients (52.1 % vs. 8.6 %; $p<0.001$). All included patients were European Caucasians.

Overall, 413 patients (49.8 %) had polypharmacy. Patients with polypharmacy were significantly older and were more likely to have concomitant active cancer, arterial hypertension, cardiac disease, cerebrovascular disease, chronic renal disease, diabetes mellitus, history of major bleeding, recent surgery, high risk of falls, and anemia than patients without polypharmacy (Table 1). They were also more likely to receive antiplatelet/non-steroidal anti-inflammatory drug therapy and preexisting vitamin K antagonist treatment, and less likely to receive thrombolytic therapy, than patients without polypharmacy.

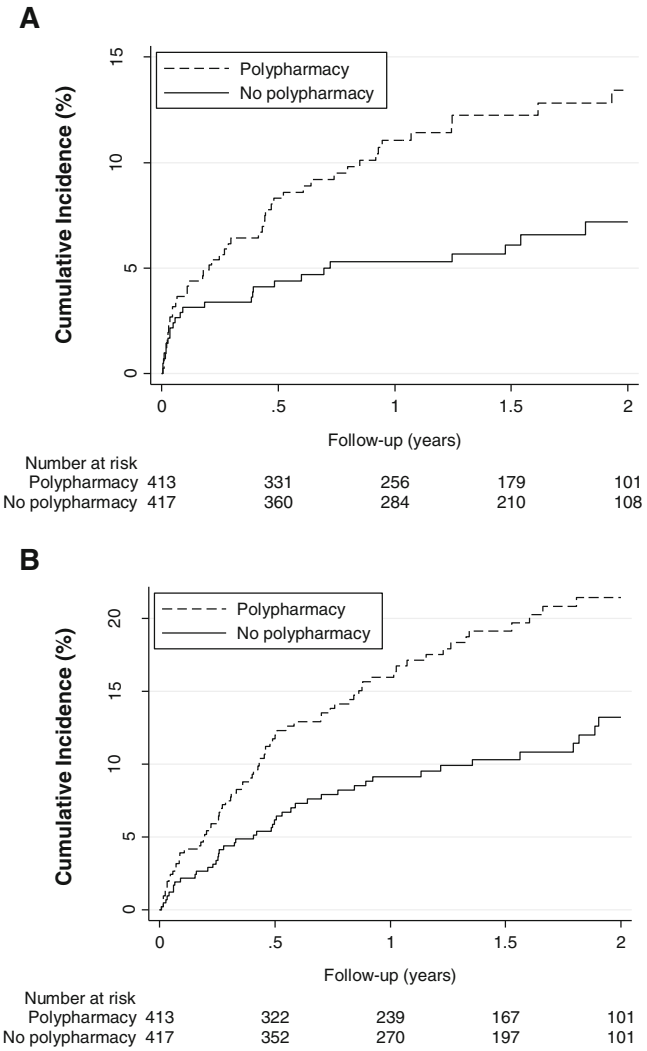

Figure 1. Panel A. Kaplan-Meier estimates for major bleeding by polypharmacy. Patients with polypharmacy had a higher 2-year cumulative incidence of major bleeding than patients without polypharmacy (13.4 % vs. 7.2 %; $p=0.002$ by the logrank test). Panel B. Kaplan-Meier estimates for clinically relevant non-major bleeding by polypharmacy. Patients with polypharmacy had a higher 2-year cumulative incidence of clinically relevant non-major bleeding than patients without polypharmacy (21.4 % vs. 13.2 %; $p<0.001$ by the logrank test).

Comparison of Bleeding

During a mean (±standard deviation) follow-up duration of 17.8 (±9.3) months following VTE, we observed 182 first bleeding episodes (75 major and 126 clinically relevant non-major bleedings); 87 patients died. Overall, six (8.0 %) major bleeds were intracranial and four (5.3 %) were fatal. The overall incidences of major and clinically relevant non-major bleeding were 6.4 and 11.3 events per 100 patient-years, respectively. Patients with polypharmacy had a significantly higher incidence of major bleeding (9.0 vs. 4.1 events per 100 patient-years; incidence rate ratio [IRR] 2.18, 95 % confidence interval [CI] 1.32–3.68) and clinically relevant non-major bleeding (14.8 vs. 8.0 events per 100 patient-years; IRR 1.85, 95 % CI 1.27–2.71) than patients without polypharmacy. As shown in Fig. 1 (Panel A and B), patients with polypharmacy had a significantly higher cumulative incidence of major and clinically relevant non-major bleedings than patients without polypharmacy.

Overall, patients spent 26.0 %, 57.4 %, and 16.6 % of time in a subtherapeutic (< 2.0), therapeutic (2.0–3.0), and supratherapeutic (> 3.0) INR range, respectively. Patients with polypharmacy spent less time in the therapeutic INR range (54.7 % vs. 60.0 %; $p<0.001$) and more time in a subtherapeutic INR range than patients without polypharmacy (27.8 % vs. 24.3 %; $p=0.02$). Overall, patients with polypharmacy spent a non-significantly higher percentage of time in a supratherapeutic INR range than patients without polypharmacy (17.5 % vs. 15.7 %; $p=0.14$).

At the time of bleeding (major and clinically relevant non-major), patients with polypharmacy were significantly more

likely to have a supratherapeutic INR value (>3.0) than patients without polypharmacy (49.2 % vs. 27.9 %; p=0.03).

Overall, 34 of 182 first bleeds (18.7 %) were fall-related. Patients with polypharmacy had a significantly higher overall incidence of a first fall-related bleeding (4.8 vs. 1.6 events per 100 patient-years; IRR 2.98, 95 % CI 1.41–6.88).

Association Between Polypharmacy and Bleeding

After adjustment for previously described bleeding risk factors and periods of vitamin K antagonist treatment as a time-varying covariate, polypharmacy was associated with the time to a first major bleeding (adjusted SHR 1.83, 95 % CI 1.03–3.25; Fig. 2) and the time to a first clinically relevant non-major bleeding (adjusted SHR 1.60, 95 % CI 1.06–2.42; Fig. 3). Besides polypharmacy, only chronic liver disease was statistically significantly associated with major bleeding (SHR 3.53, 95 % CI 1.10–11.34). After additional adjustment for antiplatelet/non-steroidal anti-inflammatory therapy, the magnitude of the association between polypharmacy and major (SHR 1.74, 95 % CI 0.96–3.14) and clinically relevant non-major bleeding (SHR 1.43, 95 % CI 0.93–2.20) decreased somewhat (Table 2).

When we further adjusted for the risk of falls, the magnitude of the association between polypharmacy and major (SHR 1.70, 95 % CI 0.94–3.08) and clinically relevant non-major bleeding (SHR 1.27, 95 % CI 0.82–1.97) decreased even more (Table 2). When we assumed missing values to be abnormal in a sensitivity analysis, the results did not change markedly.

DISCUSSION

In this prospective study of elderly patients receiving vitamin K antagonists for acute VTE, we found that after multiple adjustments, patients with polypharmacy had a significantly higher risk of major and medically relevant non-major bleeding than patients without polypharmacy. There are several potential explanations for the observed association between polypharmacy and bleeding in our study. First, patients with polypharmacy spent more time in the subtherapeutic INR range than patients without polypharmacy, indicating that drug interactions potentiating the effect of vitamin K antagonists were not the primary cause of bleeding in our study. However, patients with polypharmacy

Clinical characteristic	Adjusted sub-hazard ratio[a] (95% confidence interval)
Polypharmacy	1.83 (1.03 to 3.25)
Age (per 10 years)	1.06 (0.74 to 1.50)
Female gender	1.32 (0.80 to 2.16)
Overt pulmonary embolism	1.12 (0.66 to 1.92)
Active cancer	0.75 (0.32 to 1.77)
Arterial hypertension	0.73 (0.43 to 1.25)
Cardiac disease	1.49 (0.89 to 2.50)
Cerebrovascular disease	0.82 (0.36 to 1.84)
Chronic liver disease	3.53 (1.10 to 11.34)
Chronic renal disease	1.52 (0.87 to 2.64)
Diabetes mellitus	0.88 (0.47 to 1.66)
History of major bleeding	1.37 (0.69 to 2.71)
Recent surgery	1.14 (0.57 to 2.28)
Anemia	1.28 (0.74 to 2.21)
Thrombocytopenia	0.96 (0.49 to 1.88)

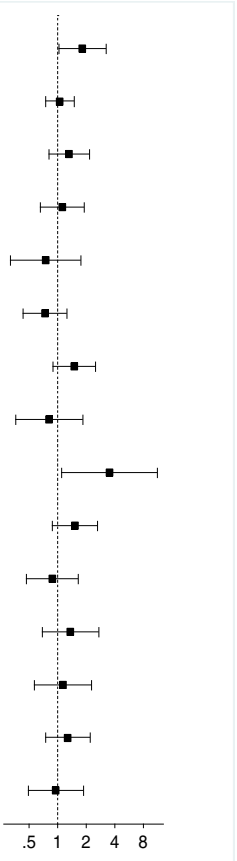

Figure 2. Association between polypharmacy and the time to a first major bleeding. Competing risk regression analysis, accounting for death as a competing risk. In addition, the model was also adjusted for periods of anticoagulation as a time-varying co-variate.

Clinical characteristic	Adjusted sub-hazard ratio[a] (95% confidence interval)
Polypharmacy	1.60 (1.06 to 2.42)
Age (per 10 years)	1.30 (0.97 to 1.74)
Female gender	0.82 (0.56 to 1.19)
Overt pulmonary embolism	1.13 (0.75 to 1.69)
Active cancer	0.92 (0.48 to 1.74)
Arterial hypertension	0.86 (0.57 to 1.28)
Cardiac disease	1.07 (0.70 to 1.63)
Cerebrovascular disease	1.07 (0.59 to 1.95)
Chronic liver disease	1.88 (0.53 to 6.66)
Chronic renal disease	1.11 (0.70 to 1.75)
Diabetes mellitus	0.99 (0.62 to 1.59)
History of major bleeding	0.92 (0.48 to 1.75)
Recent surgery	0.97 (0.52 to 1.81)
Anemia	1.22 (0.82 to 1.83)
Thrombocytopenia	1.12 (0.68 to 1.84)

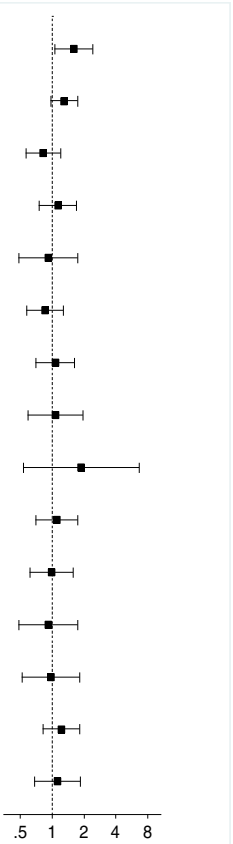

Figure 3. Association between polypharmacy and the time to a first clinically relevant non-major bleeding. [a]Competing risk regression analysis, accounting for death as a competing risk. In addition, the model was also adjusted for periods of anticoagulation as a time-varying co-variate.

were more likely to be overanticoagulated at the time of bleeding than patients without polypharmacy (49.2 vs. 27.9 %). Overall, these findings suggest that it may be difficult to maintain constant INR levels in elderly patients with polypharmacy, with brief phases of overanticoagulation potentially resulting in bleeding. Besides drug-drug interactions, other potential reasons for more instable INR values in the elderly taking multiple drugs include the requirement of lower doses of vitamin K antagonists, frequent changes in medications and vitamin K intake with intercurrent illnesses, and suboptimal adherence.[31] Second, 57.6 % of patients with polypharmacy received antiplatelet/non-steroidal anti-inflammatory drugs, compared to only 22.1 % of patients without polypharmacy in our sample. Additional adjustment for antiplatelet/non-steroidal anti-inflammatory drugs somewhat decreased the magnitude of the association between polypharmacy and bleeding, indicating that the concomitant treatment with these drugs may be a driving factor for the increased bleeding risk in anticoagulated patients who receive multiple drug treatments.

Table 2. Adjusted Models of the Association Between Polypharmacy and the Time to a First Bleeding

	Adjusted sub-hazard ratio (95 % confidence interval)		
	Base model[a]	**Base model[a] plus adjustment for antiplatelet/ NSAID therapy**	**Base model[a] plus adjustment for antiplatelet/ NSAID therapy and risk of falls**
Major bleeding			
Polypharmacy	1.83 (1.03 to 3.25)	1.74 (0.96 to 3.14)	1.70 (0.94 to 3.08)
No polypharmacy	Reference	Reference	Reference
Clinically relevant non-major bleeding			
Polypharmacy	1.60 (1.06 to 2.42)	1.43 (0.93 to 2.20)	1.27 (0.82 to 1.97)
No polypharmacy	Reference	Reference	Reference

Abbreviation: NSAIDnon-steroidal anti-inflammatory drug

[a]Competing risk regression analysis, accounting for death as a competing risk. Adjustments were made for age, gender, overt pulmonary embolism, active cancer, arterial hypertension, cardiac disease, cerebrovascular disease, chronic liver disease, chronic renal disease, diabetes mellitus, history of major bleeding, recent surgery, anemia, thrombocytopenia, and periods of vitamin K antagonist treatment as a time-varying covariate

Third, patients with polypharmacy had a higher incidence of fall-related bleeding than patients without polypharmacy in our study. When we additionally adjusted for risk of falls, the magnitude of the association between polypharmacy and bleeding decreased even more, indicating that risk of falls may account for at least some of the relationship between polypharmacy and the risk of bleeding. Overall, although polypharmacy is known to increase the risk of falls in the elderly, mainly as a result of drug-induced sedation and orthostatic hypotension,[11,32] whether an increased falls risk is associated with major bleeding remains controversial.[8,33,34] Finally, a greater number of prescribed drugs may simply reflect patients' higher comorbid burden, an independent predictor of serious bleeding.[13] Given that patients with polypharmacy were older and sicker in our study, despite extensive adjustment, we cannot exclude the possibility that the association between polypharmacy and bleeding is due to unmeasured potential confounders, such as overall comorbidity, acute illnesses, alcohol abuse, malnutrition, and genetic factors (e.g., CYP2C9 and VKORC1 gene mutations), rather than an effect of polypharmacy.

Our findings are difficult to compare with the results of prior studies that used differing definitions for polypharmacy,[6,7,33] focused on other disease populations (e.g., patients with atrial fibrillation),[4–9,33,35] and included also patients aged < 65 years.[4,5,7,8,35] While most studies found that the prescription of more than two to seven drugs[4,6–8] was significantly associated with bleeding, others did not.[33,35] In one retrospective study of 811 anticoagulated patients, of whom 74 % had mechanical heart valves or atrial fibrillation, patients who bled were not taking more medications than those who did not bleed.[35] However, the patients in this study were substantially younger than in our cohort and over 80 % received less than two co-medications. Finally, in a prospective study of 4,093 patients aged ≥ 80 years, of whom 74 % received vitamin K antagonists for atrial fibrillation, the use of ≥ 3 co-medications did not significantly increase the risk of major bleeding.[33] Of note, patients were managed by professional anticoagulation clinics in this study, resulting in a very low major bleeding rate of 1.9 events per 100 patient-years only.

Our findings have clinical and research implications. Given that elderly patients with VTE who receive vitamin K antagonists and multiple drug treatments have a higher bleeding risk, such patients could potentially benefit from a more intensive anticoagulation monitoring. It seems prudent to critically review medications and to stop concomitant treatment with antiplatelet/non-steroidal anti-inflammatory drugs and medications with an increased risk for interactions, sedation or orthostatic hypotension, if feasible. The presence of polypharmacy could also be a reason against extending vitamin K antagonist treatment beyond the duration of three months in such patients. Further studies are needed to examine by which mechanism(s) polypharmacy is potentially causally related to bleeding complications in patients receiving vitamin K antagonists. Whether new oral anticoagulants (e.g., rivaroxaban, dabigatran and apixaban) that have a lower potential for drug-drug interactions can be more safely used in elderly patients receiving multiple drug treatments should also be examined.[36]

Our study has potential limitations. First, given that our cohort included patients with VTE only, our results may not be generalizable to other indications for anticoagulant treatment. Second, all enrolled patients were European Caucasians. Thus, our results may not necessarily apply to other races/ethnicities. Third, with the exception of platelet inhibitors/non-steroidal anti-inflammatory drugs, the number and class of prescribed medications was not documented. Thus, we could not examine whether a dose–response relationship existed between the number of drugs and the bleeding risk, or whether bleeding risk was driven by specific drugs, such as antibiotics or selective serotonin or serotonin-norepinephrine reuptake inhibitors. Similarly, we had no information on the concomitant use of vitamins or alternative medicine products (except St. John's wort). Fourth, we could not assess drug adherence or whether the number of prescribed drugs changed during follow-up. Fifth, although we could adjust for the vast majority of known bleeding risk factors, we cannot exclude the possibility that the association between polypharmacy and bleeding is due to other, unmeasured confounders, such as overall comorbidity, acute illnesses, alcohol abuse, malnutrition, and genetic factors. Finally, we could only detect associations, not causality. Thus, we could not determine whether polypharmacy has a direct causal effect on bleeding, or if it is simply a marker of comorbidity.

In conclusion, elderly patients with polypharmacy who receive vitamin K antagonists for VTE may have a significantly increased risk of major and clinically relevant non-major bleeding. The need for antiplatelet/non-steroidal anti-inflammatory drugs and medications with interactions, sedative effect, and the potential to induce orthostatic hypotension should be critically reviewed in such patients. Further studies should explore by which mechanism polypharmacy increases the risk of bleeding, and whether less interacting new oral anticoagulants could decrease bleeding risk in patients with polypharmacy.

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Corresponding Author: *Waltraud Leiss, MD; Department of General Internal Medicine, Bern University Hospital, Bern, Switzerland (e-mail: Waltraud.Leiss@Insel.ch).*

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