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Long-term clinical outcomes in older patients with acute venous thromboembolism who have renal impairment

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ABSTRACT

Introduction: Renal impairment (RI) may induce an inflammatory/procoagulant state as well as platelet dysfunction. Little is known on the prevalence of RI and long-term prognosis of older patients with venous thromboembolism (VTE) who have concomitant RI.

Methods: In a prospective multicenter cohort, we analyzed 912 patients aged ≥65 years with acute VTE. Using the CKD-EPI formula, we defined three categories of baseline renal function: estimated glomerular filtration rate ≥60ml/min/1.73m^2 (no RI), 30-59ml/min/1.73m^2 (moderate RI), and <30ml/min/1.73m^2 (severe RI). The outcomes were VTE recurrence, major bleeding, and overall mortality. We examined the association between renal function and clinical outcomes using competing risk regression models, adjusting for relevant confounders and periods of anticoagulation.

Results: We followed 912 patients over a median duration of 29.6 months. Overall, 313 (34%) patients had moderate and 51 (6%) severe RI. One hundred and seven patients (12%) had VTE recurrence, 125 (14%) had major bleeding, and 186 (20%) died during follow-up. After adjustment, severe RI was associated with a 2-fold increased risk of major bleeding (sub-hazard ratio [SHR] 2.1, 95%CI 1.1-4.0) compared to no RI, but not with VTE recurrence (SHR 0.6, 95%CI 0.2-1.8) or overall mortality (hazard ratio 1.0, 95%CI 0.6-1.9). Moderate RI was not significantly associated with adverse clinical outcomes.

Conclusions: RI was common among older patients with acute VTE. Severe RI was associated with a 2-fold increased long-term risk of major bleeding, without a risk increase in terms of VTE recurrence and overall mortality. Older patients with moderate RI did not carry worse prognosis.

Keywords

Anticoagulation, elderly, prognosis, renal impairment, venous thromboembolism

Abbreviations

AC, anticoagulation

CI, confidence interval

CKD, chronic kidney disease

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation

CRP, C-reactive protein

cTnT, cardiac troponin T

DOAC(s), direct oral anticoagulant(s)

DVT, deep vein thrombosis

(e)GFR, (estimated) glomerular filtration rate

Fig, Figure

HR, hazard ratio

INR, International Normalized Ratio

IQR, interquartile range

LMWH, low-molecular-weight heparin

MDRD, Modification of Diet in Renal Disease

NSAID(s), non-steroidal anti-inflammatory drug(s)

PE, pulmonary embolism

PESI, pulmonary embolism severity index

RI, renal impairment

SHR, sub-hazard ratio

SWITCO65+, SWIss venous Thromboembolism COhort study 65+

UFH, unfractionated heparin

U.S., United States

VKA(s), vitamin K antagonist(s)

VTE, venous thromboembolism

INTRODUCTION

The risk of venous thromboembolism (VTE) and renal impairment (RI), defined as a glomerular filtration rate (GFR) <60ml/min/1.73m^2, both increase with age [1, 2], and both conditions appear to be interconnected [3]. Chronic kidney disease (CKD) may induce an inflammatory und procoagulant state, potentially increasing the risk of VTE [4, 5]. Patients with VTE who have concomitant RI have also an increased risk of bleeding complications [6-8], possibly due to comorbid conditions [6], antithrombotic comedications [8], and platelet dysfunction [5]. Many anticoagulants, including low-molecular-weight heparins, fondaparinux, and direct oral anticoagulants (DOACs), are at least partially renally eliminated [9], and the risk of drug accumulation and subsequent bleeding increases in RI [10, 11]. RI may also affect the pharmacokinetics of vitamin K antagonists (VKAs) by decreasing plasma protein-binding and inhibiting cytochrome P450 and thus hepatic clearance [12-14].

Although the majority of patients with acute VTE are aged ≥65 years and RI is more prevalent in the elderly [15, 16], older patients are often excluded from clinical treatment trials [17], and there is little evidence on the prevalence of RI and long-term prognosis of older patients with VTE who have RI. To fill this gap of knowledge, we assessed the prevalence of RI and compared long-term clinical outcomes by renal function in a multicenter prospective cohort study of older patients with acute VTE.

METHODS

Cohort sample

The study was conducted between September 2009 and December 2013 as part of the SWIss venous Thromboembolism COhort study 65+ (SWITCO65+), a prospective multicenter cohort study of consecutive in- and outpatients aged ≥65 years with acute symptomatic objectively confirmed pulmonary embolism (PE) and/or deep vein thrombosis (DVT). The patients were enrolled from all five Swiss university and four high-volume non-university hospitals and followed up to assess long-term clinical outcomes in elderly patients with VTE. DVT was defined as the incomplete compressibility of a venous segment on ultrasonography or an intraluminal filling defect on contrast venography [18]. For iliac and caval DVT, 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. PE was defined as a positive computed tomography or pulmonary angiography, a high-probability ventilation-perfusion scan, or a proximal DVT confirmed by compression ultrasonography or contrast venography in patients with acute chest pain, new or worsening dyspnea, hemoptysis, or syncope [18]. Exclusion criteria included catheter-related thrombosis, thrombosis at a different site than lower limb, insufficient German or French-speaking ability, impracticable follow-up (i.e., terminal illness), inability to provide informed consent (i.e., severe dementia), or previous enrollment in the cohort. A detailed description of the study methods was published elsewhere [18]. The Institutional Review Board at each participating center approved the study and all patients provided written informed consent.

Baseline data collection

For all enrolled patients, trained study nurses prospectively collected information about baseline demographics (age, sex, body mass index), type (cancer-related, provoked, unprovoked) and localization of index VTE event (PE with or without DVT, isolated proximal DVT, isolated distal DVT), comorbid conditions and history findings (history of VTE, active cancer, history of recent major surgery, history of major bleeding, arterial hypertension, diabetes mellitus, chronic heart failure, cerebrovascular disease, chronic liver disease, chronic renal disease, physical activity level, risk of falls, average weekly alcohol consumption, and smoking status), systolic blood pressure at presentation, laboratory findings (hemoglobin, platelet counts, D-dimer, ultra-sensitive cardiac troponin T [cTnT], and high-sensitive C-reactive protein [CRP]), baseline medications (concomitant antiplatelet therapy or non-steroidal anti-inflammatory drugs [NSAIDs], and polypharmacy), and VTE-related treatments (type of parenteral anticoagulant, thrombolysis, thromboembolectomy, insertion of a vena cava filter, and subsequent VKA therapy) using standardized data collection forms. VTE was defined as cancer-related if it occurred the context of active cancer. VTE in the context of major surgery, estrogen therapy, or immobilization (bed rest >72 hours, fracture or cast of the lower extremity, voyage in sitting position >6 hours) within three months of the index VTE was defined as provoked. All other VTE episodes were considered unprovoked.

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. Polypharmacy was defined as the prescription of ≥5 drugs, including St. John's wort [20]. 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. The type and duration of anticoagulation, as well as the site of initial management, were left to the discretion of the managing physicians.

Renal function

We estimated the glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI), which is based on patient age, sex, race, and serum creatinine measured at the time of the diagnosis of the index VTE [21]. We used the CKD-EPI method rather than the Modification of Diet in Renal Disease (MDRD) and Cockcroft-Gault formula because it was shown to be more accurate at estimating renal function in older adults [22-24]. In addition, the MDRD formula systematically underestimates the GFR in individuals with a normal or mildly reduced renal function whereas the commonly used Cockcroft-Gault formula overestimates the GFR, especially at low GFRs [23]. In patients with VTE, the CKD-EPI and Cockroft-Gault formula are discordant in more than 40% of cases regarding the presence of severe RI [8]. For the purpose of this study, we defined three simplified categories of renal function based on the eGFR: ≥60ml/min/1.73m^2 (no RI), 30-59ml/min/1.73m^2 (moderate RI), and <30ml/min/1.73m^2 (severe RI).

Study outcomes

Our study outcomes were adverse clinical events, i.e., VTE recurrence, major bleeding, and overall mortality within 36 months of follow-up. VTE recurrence was defined as a new or recurrent, symptomatic, objectively confirmed PE and/or DVT (proximal and/or distal), as previously described [18]. Major bleeding was defined as fatal bleeding, symptomatic bleeding at critical sites (intracranial, intra-spinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular with

compartment syndrome), or bleeding with a reduction of hemoglobin of at least 20 g/L or bleeding leading to transfusion of 2 or more units of packed red blood cells [25]. In the subgroup of patients treated with VKAs, we also explored the quality of anticoagulation, expressed as the percentage of time spent in a given International Normalized Ratio (INR) range (<2.0, 2.0–3.0, and >3.0) according to Rosendaal [26].

Follow-up included one telephone interview and two face-to-face evaluations during the first year of study and then semi-annual contacts, alternating between face-to-face evaluations and telephone calls, as well as periodic hospital chart reviews. As part of the follow-up interviews/visits, study nurses obtained information about the date and type of VTE recurrence, bleeding events, and death. If a clinical event had occurred, this information was complemented by reviewing medical charts and interviewing patients' primary care physicians and/or family members.

An independent committee of three experienced general internists adjudicated all outcomes and classified the causes of death as definitely due to PE (i.e., confirmed by autopsy or death following a clinically severe PE), possibly due to PE (i.e., sudden or unexpected death), due to major bleeding (e.g., death after intracranial hemorrhage or hemodynamic deterioration following a major bleeding) [27], or due to another cause. The adjudicators were blinded to patient characteristics and treatments received. The final classification was based on full consensus of the committee.

Statistical analyses

We compared patient baseline characteristics by renal function using Chi-squared and non-parametric Kruskal–Wallis tests as appropriate. We estimated the 36-month cumulative incidence rate of VTE recurrence, major bleeding, and overall mortality using the Kaplan-Meier method and compared survivor functions across

renal function categories by the log-rank test. We examined the association between renal function and the time to a first VTE recurrence and major bleeding using competing risk regression models according to Fine and Gray [28], accounting for non-VTE or bleeding-related death as a competing event. The strength of the association between renal function and adverse clinical outcomes 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 have been previously shown to be independently associated with recurrent VTE (age, sex, body mass index, type [provoked or unprovoked] and localization of the index VTE [PE ± concomitant DVT, proximal DVT only, distal DVT only], history of VTE, and active cancer) [29-33] or major bleeding (age, sex, active cancer, recent major surgery, history of major bleeding within three months before the index VTE, history of arterial hypertension, diabetes mellitus, cerebrovascular disease, chronic liver disease, low physical activity level (i.e., mostly lying/sitting activity or avoidance to climb stairs or carry light weight [<5 kg]), risk of falls, anemia, low platelet count, and concomitant use of antiplatelet therapy or NSAIDs) [34-39]. We examined the association between renal function and the time to death using Cox regression with robust standard errors, adjusting for confounders identified by a prior study, i.e., age, active cancer, diabetes mellitus, physical activity level, systolic blood pressure, anemia, D-dimer, ultra-sensitive cTnT, and high-sensitive CRP [40]. All three regression models were adjusted for 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 renal function status.

For the subgroup of patients treated with VKA, we compared the percentage of time spent below (<2.0), within (2.0–3.0), and above (>3.0) the therapeutic INR range by renal function (excluding the first seven days of treatment) and examined the

association between quality of anticoagulation and renal function using linear regression, adjusting for known determinants of anticoagulation quality (age, sex, body mass index, active cancer, diabetes mellitus, chronic heart failure, chronic liver disease, low physical activity level, self-reported average weekly alcohol consumption, smoking status, and polypharmacy) [41-44]. We performed multiple imputations for missing values for body mass index, history of major bleeding, physical activity level, risk of falls, alcoholic drinks/week, smoking status, systolic blood pressure, anemia, thrombocytopenia, D-dimer, ultra-sensitive cTnT, and high-sensitive CRP. Imputation models were based on all other risk factor variables as well as an indicator variable for VTE recurrence, major bleeding, death, and hospital site resulting in fifty imputed data sets, which were analyzed using Rubin's rules to combine results across data sets. The exact definitions of all co-variates are shown in Table 1. All analyses were done using Stata 16 (Stata Corporation, College Station, Texas). A two-sided *p* value <0.05 was considered statistically significant.

RESULTS

Study sample

Of the 1003 patients enrolled in SWITCO65+, we excluded 79 because the eGFR was not available and 12 who withdrew early or denied the use of their data, leaving a final study sample of 912 patients with acute VTE. The median age (75.0 years [interquartile range (IQR) 69.0–81.0] vs. 75.0 years [IQR 69.0–79.0], p=0.394) and female sex (47% vs. 43%, p=0.557) did not differ between patients with available eGFR and missing eGFR. The median duration of initial anticoagulation and follow-up was 7.8 months (IQR 4.1–24.0) and 29.6 months (IQR 18.1–36.2), respectively. The duration of initial anticoagulation did not differ significantly by renal function (data not shown).

Overall, 548 patients (60%) had an eGFR ≥60ml/min/1.73m^2, 313 (34%) an eGFR 30-59ml/min/1.73m^2, and 51 (6%) an eGFR <30ml/min/1.73m^2. Patients with an eGFR <60ml/min/1.73m^2 were older than those with an eGFR ≥60ml/min/1.73m^2 (78.0 vs. 73.0 years), and were more likely to have a history of arterial hypertension, diabetes mellitus, chronic heart failure, a low physical activity level, an increased risk of falls, arterial hypotension (i.e., a systolic blood pressure <100 mm Hg at the time of VTE diagnosis), anemia, a higher PESI score, an elevated ultra-sensitive cTnT and high-sensitive CRP, antiplatelet/NSAIDs therapy, and polypharmacy (**Table 1**). As expected, the prevalence of known chronic renal disease increased from 5% among patients with an eGFR ≥60ml/min/1.73m^2 to 73% among those with an eGFR <30ml/min/1.73m^2. Patients with an eGFR <60ml/min/1.73m^2 were also more likely to receive unfractionated heparin than low-molecular-weight heparin as the initial parenteral anticoagulation. Conversely, patients with an eGFR ≥60ml/min/1.73m^2 were more likely to have a history of major surgery during the last 3 months and a higher consumption of alcoholic drinks per week than those with a reduced eGFR.

Table 1. Patient baseline characteristics and treatments by renal function

	All (N=912)	eGFR ≥60ml/min/1.73m² (N=548)	eGFR 30-59ml/min/1.73m² (N=313)	eGFR <30ml/min/1.73m² (N=51)	p-value
Characteristics*	**n (%) or median (interquartile range)**				
Age, years	75 (69-81)	73 (68-78)	78 (72-84)	78 (70-84)	<0.001
Female sex	429 (47)	242 (44)	160 (51)	27 (53)	0.099
Body mass index, kg/m²	27 (24-30)	26 (24-30)	27 (24-31)	26 (24-30)	0.012
Type of index VTE					0.304
Cancer-related VTE	172 (19)	107 (20)	56 (18)	9 (18)	
Provoked VTE†	198 (22)	130 (24)	57 (18)	11 (22)	
Unprovoked VTE‡	542 (59)	311 (57)	200 (64)	31 (61)	
Localization of index VTE					0.950
PE ± DVT	674 (74)	403 (74)	233 (74)	38 (75)	
Proximal DVT only	175 (19)	104 (19)	61 (19)	10 (20)	
Distal DVT only	63 (7)	41 (7)	19 (6)	3 (6)	
History of VTE	256 (28)	141 (26)	103 (33)	12 (24)	0.060
Active cancer¶	172 (19)	107 (20)	56 (18)	9 (18)	0.819
Major surgery#	141 (15)	101 (18)	34 (11)	6 (12)	0.010
History of major bleeding§	46 (5)	30 (5)	15 (5)	1 (2)	0.529
Arterial hypertension	595 (65)	309 (56)	244 (78)	42 (82)	<0.001
Diabetes mellitus	149 (16)	75 (14)	57 (18)	17 (33)	0.001
Chronic heart failure‖	72 (8)	35 (6)	27 (9)	10 (20)	0.003
Cerebrovascular disease**	89 (10)	48 (9)	32 (10)	9 (18)	0.116
Chronic liver disease††	14 (2)	12 (2)	1 (0)	1 (2)	0.097
Chronic renal disease‡‡	182 (20)	29 (5)	116 (37)	37 (73)	<0.001
Low physical activity¶¶	347 (38)	178 (32)	142 (45)	27 (53)	<0.001
Increased risk of falls##	436 (48)	242 (44)	167 (53)	27 (53)	0.020
Alcoholic drinks/week, no.§§	2 (0-7)	2 (0-7)	1 (0-7)	0 (0-5)	<0.001
Current or past smoker	445 (49)	272 (50)	149 (48)	24 (47)	0.844
Arterial hypotension‖‖	34 (4)	22 (4)	7 (2)	5 (10)	0.027
Anemia***	380 (42)	211 (39)	137 (44)	32 (63)	0.003
Thrombocytopenia†††	136 (15)	79 (14)	48 (15)	9 (18)	0.809
PESI, points	94 (80-113)	89.5 (78-111)	97 (84-114)	98 (82-114)	0.001
D-dimer >3000 ng/ml	307 (34)	188 (34)	102 (33)	17 (33)	0.995
Ultra-sensitive cTnT >14 pg/mL	414 (45)	200 (36)	174 (56)	40 (78)	<0.001
High-sensitive CRP >40 mg/L	303 (33)	198 (36)	82 (26)	23 (45)	0.006
Antiplatelet/NSAID therapy‡‡‡	347 (38)	182 (33)	146 (47)	19 (37)	<0.001
Polypharmacy¶¶¶	478 (52)	256 (47)	189 (60)	33 (65)	<0.001
Initial parenteral AC					<0.001
LMWH	416 (46)	273 (50)	131 (42)	12 (24)	
UFH	322 (35)	163 (30)	124 (40)	35 (69)	
Other###	143 (16)	91 (17)	49 (15)	3 (6)	
None	31 (3)	21 (4)	9 (3)	1 (2)	
Thrombolysis§§§	30 (3)	20 (4)	9 (3)	1 (2)	0.713
Thromboembolectomy	3 (0)	3 (1)	0 (0)	0 (0)	0.368
Inferior vena cava filter	11 (1)	8 (1)	2 (1)	1 (2)	0.500
Subsequent VKA therapy‖‖‖	789 (87)	471 (86)	272 (87)	46 (90)	0.676

Abbreviations: eGFR, estimated glomerular filtration rate; VTE, venous thromboembolism; PE, pulmonary embolism; DVT, deep vein thrombosis; PESI, pulmonary embolism severity index; cTnT, cardiac troponin T; CRP, C-reactive protein; NSAID, non-steroidal anti-inflammatory drug; AC, anticoagulation; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; VKA, vitamin K antagonist.

*Data were missing for body mass index (n=5, 0.5%), history of major bleeding (n=1, 0.1%), low physical activity level (n=3, 0.3%), risk of falls (n=2, 0.2%), number of alcoholic drinks/week (n=7, 0.8%), smoking status (n=3, 0.3%), arterial hypotension

(n=6, 0.7%), anemia (n=5, 0.5%), thrombocytopenia (n=6, 0.7%), D-dimer (n=132, 14%), ultra-sensitive cTnT (n=116, 13%), and high-sensitive CRP (n=112, 12%).

†Major surgery, estrogen therapy, or immobilization (bed rest >72 hours, fracture or cast of the lower extremity, voyage in sitting position >6 hours) during the last 3 months before the index VTE.

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

¶Leukemia, lymphoma, or non-metastatic solid cancer requiring chemotherapy, radiotherapy, surgery, or palliative care during the last 3 months, excluding local skin tumors such as basal cell carcinoma and spinal cell carcinoma.

#Surgery requiring general or spinal anesthesia during the last 3 months.

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

‖Systolic or diastolic heart failure, left or right heart failure, forward or backward heart failure, or a known left ventricular ejection fraction of <40%.

**History of ischemic or hemorrhagic stroke or transient ischemic attack at the time of screening.

††Liver cirrhosis, chronic hepatitis (B, C, autoimmune, etc.), chronic liver failure**,** or hemochromatosis.

‡‡Chronic renal failure requiring or not hemodialysis such as diabetic or hypertensive nephropathy, chronic glomerulonephritis, chronic interstitial nephritis, myeloma-related nephropathy, or cystic kidney disease.

¶¶Mostly lying/sitting activity or avoidance to climb stairs or carry light weight (<5 kg).

##Self-reported fall during the last year or any problem with gait, balance, or mobility.

§§Self-reported average weekly standardized amount of alcoholic beverages during last 12 months.

‖‖Systolic blood pressure <100 mm Hg at the time of diagnosis of the index VTE.

***Hemoglobin <130 g/L in men or <120 g/L in women.

†††Thrombocytes <150 G/L.

‡‡‡Use of any antiplatelet therapy, such as aspirin, clopidogrel, prasugrel, aspirin/dipyridamole, or NSAIDs.

¶¶¶Defined as a current prescription of ≥5 different drugs, including St. John's wort.

###Fondaparinux or danaparoid.

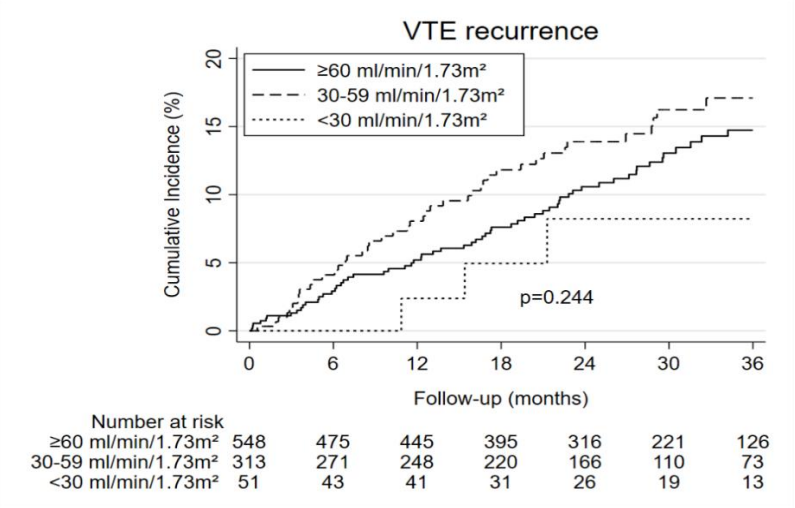
§§§Catheter-directed or systemic thrombolysis.

‖‖‖‖‖Among the 123 patients who did not receive subsequent VKAs, 52% received treatment with LWMH, 30% with UFH, 11% with fondaparinux, and 7% no anticoagulation.

Renal function and adverse clinical events

One hundred and seven patients (12%) had a VTE recurrence, 125 (14%) a major bleeding within 36 months of follow-up, and 186 (20%) died. Of these, 32 (17%) died from PE and 13 (7%) from bleeding. While the 36-month cumulative incidence of VTE recurrence and overall mortality did not differ by renal function (**Fig. A and C**), the cumulative 36-month incidence of major bleeding increased with decreasing renal function, from 12.6% (95% confidence interval [CI] 9.9-16.0%) in patients with an eGFR ≥60ml/min/1.73m^2 to 30.2% (95%CI 17.6-48.7%) in patients with an eGFR <30ml/min/1.73m^2 (p=0.005 by the log-rank test) (**Fig. B**). Of the 125 major bleedings, 36 (29%) occurred within 30 days of the index VTE.

Figure A

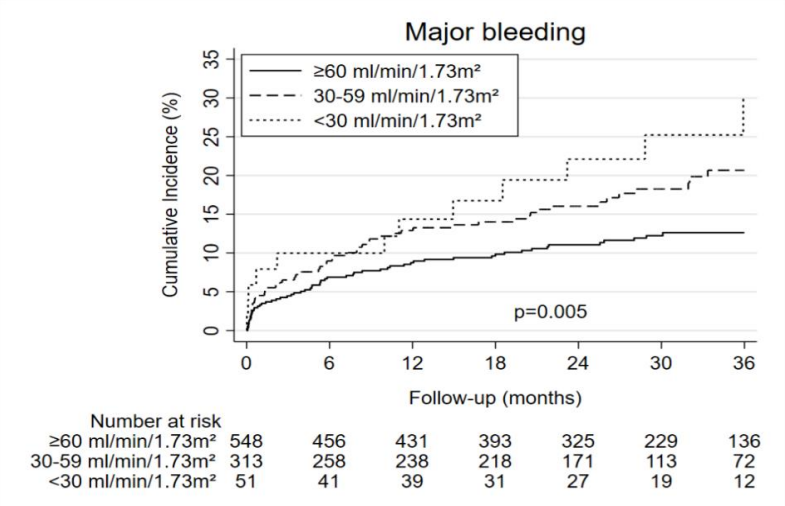


Abbreviations: eGFR, estimated glomerular filtration rate; VTE, venous thromboembolism; CI, confidence interval.

Kaplan-Meier estimates of recurrent VTE by renal function

The 36-month cumulative incidence of a first recurrent VTE was 14.7% (95%CI 11.5-18.7%) in patients with an eGFR ≥60ml/min/1.73m^2, 17.1% (95%CI 12.8-22.6%) in patients with an eGFR 30-59ml/min/1.73m^2, and 8.2% (95%CI 2.7-23.7%) in patients with an eGFR <30ml/min/1.73m^2 (p=0.244 by the log-rank test).

Figure B

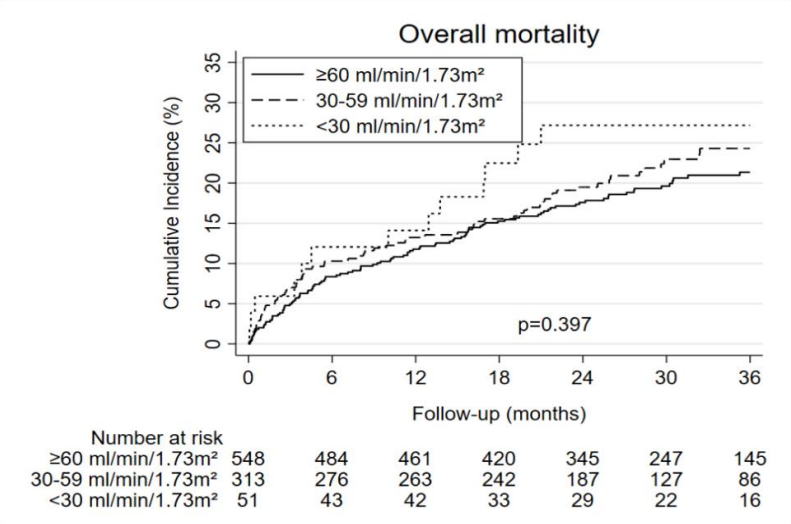


Abbreviations: eGFR, estimated glomerular filtration rate; CI, confidence interval.

Kaplan-Meier estimates of major bleeding by renal function

The 36-month cumulative incidence of a first major bleeding was 12.6% (95%CI 9.9-16.0%) in patients with an eGFR ≥60ml/min/1.73m^2, 20.7% (95%CI 15.9-26.6%) in patients with an eGFR 30-59ml/min/1.73m^2, and 30.2% (95%CI 17.6-48.7%) in patients with an eGFR <30ml/min/1.73m^2 (p=0.005 by the log-rank test).

Figure C



Abbreviations: eGFR, estimated glomerular filtration rate; CI, confidence interval.

Kaplan-Meier estimates of death by renal function

The 36-month cumulative incidence of death was 21.3% (95%CI 17.9-25.4%) in patients with an eGFR ≥60ml/min/1.73m^2, 24.3% (95%CI 19.5-30.0%) in patients with an eGFR 30-59ml/min/1.73m^2, and 27.2% (95%CI 16.7-42.3%) in patients with an eGFR <30ml/min/1.73m^2 (p=0.397 by the log-rank test).

After adjustment for known risk factors of bleeding, patients with eGFR <30ml/min/1.73m^2 had 2-fold higher risk of major bleeding (adjusted SHR 2.1, 95%CI 1.1-4.0) compared to patients with an eGFR ≥60ml/min/1.73m^2 (**Table 2**). Renal function was not independently associated with recurrent VTE or overall mortality.

Table 2. Association between renal function and adverse clinical events

Adverse clinical events	**Crude SHR (95%CI)**	**p-value**	**Adjusted SHR* (95%CI)**	**p-value**
VTE recurrence				
eGFR ≥60ml/min/1.73m^2	Ref.		Ref.	
eGFR 30-59ml/min/1.73m^2	1.3 (0.9 - 1.9)	0.25	1.4 (0.9 - 2.0)	0.14
eGFR <30ml/min/1.73m^2	0.5 (0.2 - 1.7)	0.27	0.6 (0.2 - 1.8)	0.32
	Crude SHR (95%CI)	**p-value**	**Adjusted SHR† (95%CI)**	**p-value**
Major Bleeding				
eGFR ≥60ml/min/1.73m^2	Ref.		Ref.	
eGFR 30-59ml/min/1.73m^2	1.6 (1.1 - 2.3)	0.02	1.5 (1.0 - 2.2)	0.06
eGFR <30ml/min/1.73m^2	2.3 (1.3 - 4.3)	0.01	2.1 (1.1 - 4.0)	0.03
	Crude HR (95%CI)	**p-value**	**Adjusted HR‡ (95%CI)**	**p-value**
Overall mortality				
eGFR ≥60ml/min/1.73m^2	Ref.		Ref.	
eGFR 30-59ml/min/1.73m^2	1.1 (0.8 - 1.6)	0.38	0.9 (0.6 - 1.2)	0.43
eGFR <30ml/min/1.73m^2	1.4 (0.8 - 2.5)	0.23	1.0 (0.6 - 1.9)	0.91

Abbreviations: VTE, venous thromboembolism; SHR, sub-hazard ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio.

*Adjusted for age, sex, body mass index, provoked/unprovoked VTE, localization of index VTE, history of VTE, active cancer, periods of anticoagulation as a time-varying covariate, and competing risk of death.

†Adjusted for age, sex, active cancer, recent major surgery, history of major bleeding, arterial hypertension, diabetes mellitus, cerebrovascular disease, chronic liver disease, low physical activity, high risk of falls, anemia, thrombocytopenia, concomitant antiplatelet/non-steroidal anti-inflammatory therapy, periods of anticoagulation as a time-varying covariate, and competing risk of death.

‡Adjusted for age, active cancer, diabetes mellitus, physical activity level, systolic blood pressure, anemia, D-dimer, ultra-sensitive troponin, high-sensitive C-reactive protein, and periods of anticoagulation as a time-varying covariate.

Renal function and quality of oral anticoagulation

We assessed the quality of oral anticoagulation in 767 of 912 patients (84%) who received VKAs and for whom INR values were available. Although patients with an eGFR <30ml/min/1.73m^2 tended to spend slightly less time in the subtherapeutic (<2.0) and therapeutic INR range (2.0-3.0) and slightly more time in the supratherapeutic INR range (>3.0) than patients with an eGFR ≥60ml/min/1.73m^2, the differences did not achieve statistical significance (**Table 3**).

Table 3. Quality of oral anticoagulation by renal function*

Percentage of time spent in a given INR range†	Adjusted‡ mean difference of % of time (95%CI)	p-value
< 2.0		
eGFR ≥60ml/min/1.73m^2	Ref.	
eGFR 30-59ml/min/1.73m^2	-0.9 (-4.4 to 2.5)	0.59
eGFR <30ml/min/1.73m^2	-1.9 (-8.7 to 4.9)	0.58
2.0–3.0		
eGFR ≥60ml/min/1.73m^2	Ref.	
eGFR 30-59ml/min/1.73m^2	-0.0 (-3.6 to 3.5)	0.99
eGFR <30ml/min/1.73m^2	-2.0 (-8.9 to 5.0)	0.58
> 3.0		
eGFR ≥60ml/min/1.73m^2	Ref.	
eGFR 30-59ml/min/1.73m^2	1.0 (-1.8 to 3.7)	0.49
eGFR <30ml/min/1.73m^2	3.8 (-1.5 to 9.2)	0.16

Abbreviations: INR, international normalized ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate.

*In the subgroup of 767 patients who were treated with vitamin K antagonists.

†All periods of oral anticoagulation were considered excluding INR values obtained during the first seven days of each treatment period.

‡Adjusted for age, sex, body mass index, active cancer, diabetes mellitus, chronic heart failure, chronic liver disease, low physical activity, number of alcoholic drinks/week, smoking status, and polypharmacy.

DISCUSSION

In our prospective cohort of elderly patients with VTE, 34% had moderate and 6% had severe RI. After adjustment for confounders, patients with severe RI had a 2-fold higher risk of major bleeding than patients with no RI. VTE recurrence and mortality did not differ by renal function. Furthermore, we found no association between renal function and anticoagulation quality in patients treated with VKAs.

The prevalence of RI in our sample was almost 2-fold higher than in the Swiss population aged ≥60 years (25.4%) [45]. Prior registry/retrospective studies of younger patients with VTE found a prevalence of moderate and severe RI of 12-30% and 6-12%, respectively [6, 46-48]. These differences are explainable by differing patient characteristics and formulas used to estimate the GFR. Our findings are consistent with the Worcester Venous Thromboembolism Study which, like ours, enrolled older patients (mean age 66 years) and used the CKD-EPI formula to estimate the GFR [6]. Overall, 29% of patients had moderate and 8% had severe RI in the Worcester study. In the prospective GARFIELD-VTE registry, patients aged >65 years had a prevalence of moderate/severe RI of 36% based on the MDRD formula [49].

Several studies reported an association between severe RI and the risk of a first VTE [50-52]. In an individual participant meta-analysis including 95,154 persons from community-based prospective cohort studies, both a reduced eGFR and an increased albumin-creatinine ratio were independently associated with a first VTE, with persons with an eGFR of 30ml/min/1.73m^2 having a 2-fold higher risk for VTE than those with an eGFR of 100ml/min/1.73m^2 [3].

Why CKD increases the risk of VTE remains uncertain. The association between the nephrotic syndrome and VTE has been known for a long time [53]. CKD-induced activation of inflammation and procoagulation may have a causal role

in VTE [4, 5]. Inflammation markers, such as the C-reactive protein and fibrinogen, and the hemostatic markers factor VIII and von Willebrand factor are elevated in RI and could mediate the association between kidney function and VTE [54-56].

Whether RI is also associated with an elevated risk of recurrent VTE, is controversial. A European registry study found a 7-fold increase in the short-term risk of fatal PE in patients with severe RI but another did not [46, 57]. In the Worcester Venous Thromboembolism Study, patients with severe RI had a 2-fold increased recurrence risk within 36 months of the index VTE [6], possibly be due to comorbid conditions and interruptions of initial anticoagulation following bleeding. Indeed, 27% of patients with severe RI were discharged without anticoagulation in the Worcester study. In the international prospective GARFIELD-VTE registry, moderate/severe RI was associated with a 1.4-fold risk increase in recurrence within 12 months [49]. However, the GFR could not be estimated in 16% of patients in this registry.

We did not observe an association between renal function and recurrent VTE in our cohort of older patients. Although patients with severe RI were more likely to have comorbid conditions, only 10% were discharged without anticoagulant therapy in our study, suggesting that anticoagulation practices rather than comorbidity or CKD-related causes may drive the VTE recurrence risk in patients with RI.

After adjustment for bleeding risk factors, we found a 2-fold increased long-term risk of major bleeding in patients with severe RI compared to those with an eGFR ≥60ml/min/1.73m^2. The increased bleeding risk did not seem to be related to overanticoagulation, as patients with severe RI spent only a marginally longer time in the supratherapeutic INR range. The increased bleeding risk may be due to RI-induced platelet dysfunction or initial therapy with low-molecular-weight heparin [5, 10]. Although low-molecular-weight heparins are contraindicated in patients with severe RI because they are renally excreted and double the risk of major bleeding

[10, 58], one fifth of patients with severe RI initially received low-molecular-weight heparins in our sample. Our results are consistent with findings from prior studies that reported an increased short- and long-term bleeding risk in patients with VTE who had severe RI [6, 57]. Moderate RI was not associated with an elevated bleeding risk.

In contrast to prior studies of younger patients with VTE [6, 46, 49, 57], severe RI was not independently associated with overall mortality. It is possible that age per se and other comorbid conditions (e.g., cancer) rather than RI drive the mortality risk in the elderly with VTE [40], at least within the first 36 months of the index VTE.

Our study has several limitations. First, as risk factors for complications may differ between older and younger persons with VTE [40, 59, 60], our results may not necessarily be generalizable to younger patients. Second, as in other prior studies on the prognosis of renal function in VTE [6, 46, 57], the eGFR was based on a single estimation at the time of the index VTE and we could not examine whether eGFR changes over time have an impact on outcomes. Also, the number of patients with severe RI was relatively limited (n=51). However, because 73% of patients with severe RI had a history of CKD, most patients with severe RI probably had a permanently reduced eGFR. Third, we could not study the prognostic effect of albuminuria (a known risk factor for VTE) [3] or end-stage renal disease, which may represent a high-risk group for thrombotic complications [61]. Fourth, our results may be affected by residual confounding, a risk that is inherent in all cohort studies. Finally, our cohort was established in the pre-DOAC era, which made it impossible to examine the influence of DOAC use on outcomes. Guidelines favor DOACs over VKA in patients with VTE [62, 63], with the exception of severe RI, as patients with a creatinine clearance <25-30ml/min were excluded from clinical trials. Limited

evidence suggests that several DOACs may be at least as safe or even safer as VKAs in severe RI [64-66].

In conclusion, elderly patients with severe RI who received heparin and VKAs for acute VTE had a 2-fold increased long-term risk of major bleeding compared to those with a normal renal function, with a comparable risk in terms of VTE recurrence and mortality. Differences in the quality of oral anticoagulation did not appear to be responsible for the increased bleeding risk. Moderate RI was not associated with adverse outcomes. While older patients with VTE who have severe RI may potentially benefit from closer surveillance or a shorter anticoagulation duration, those with moderate RI do not appear to carry a higher risk of complications.

AUTHOR CONTRIBUTIONS

D. Aujesky was responsible for study concept and design. M. Messi, C. Beneyto Afonso and D. Aujesky wrote the manuscript. O. Stalder performed the statistical analyses. O. Stalder, M. Méan, M. Righini, and N. Rodondi revised the manuscript. M. Méan and D. Aujesky collected the data and obtained funding from the Swiss National Science Foundation. All authors revised the results and approved the final version of the manuscript.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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2. revision of the manuscript entitled 'Long-term clinical outcomes in older patients with acute venous thromboembolism who have renal impairment' (TR-D-22-00292)

Dear Dr. Bates:

We thank you again for inviting us to revise our above referenced manuscript. Below, we provide the response to the Reviewer #2 comment (re-stated in **bold**, followed by our answer).

Reviewer #2:

I suggest the authors use a clinical prognostic model to describe case severity, such as the PESI.

As suggested by the Reviewer, we added the PESI to the revised baseline Table 1.

We would like to thank you again and we hope that our manuscript is now considered suitable for publication.

On behalf of the authors,

Carlota Beneyto Afonso, MD