Il rischio emorragico nell'anziano anticoagulato per trombosi venosa profonda (TEV)

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Disclosures of: B. Cosmi

Employment	No conflict of interest to disclose
Research support	No conflict of interest to disclose
Scientific advisory board	No conflict of interest to disclose
Consultancy	No conflict of interest to disclose
Speakers bureau	Daiichi Sankyo, Janssen
Major stockholder	No conflict of interest to disclose
Patents	No conflict of interest to disclose
Honoraria	No conflict of interest to disclose
Travel support	No conflict of interest to disclose
Other	No conflict of interest to disclose

Bleeding risk during anticoagulation for VTE in the elderly Overview

- Rate
- Risk factors
- Available bleeding scores
- Usefulness of available bleeding scores

Incidence of bleeding during anticoagulation for VTE in the elderly

- variable

different settings, populations and bleeding severity classification criteria

- lower rates in RCTs than in observational studies

Elderly pts, those with active bleeding or bleeding risk factors excluded from RCTs

- possibly higher in VTE than in AF

more comorbid conditions and newly started patients on short duration therapy

- risk of major bleeding is different between VKA and DOACs

Bleeding Risk in Very Old Patients on Vitamin K Antagonist Treatment: Results of a Prospective Collaborative Study on Elderly Patients Followed by Italian Centres for Anticoagulation (EPICA)

	Distribution of Bleeding Events in Relation to Indication to Vitamin K Antagonist Treatment		
	All (pt. n. 4093)	FA (pt n. 3015)	VTE (pt. n 1078)
Age: median (range y)	84 (80–102)	83 (80–102)	84 (80–98)
Time in therapeutic range %(IQR) Time below Time above	62 (49–75) 24 (13–35) 11 (5–18)	63 (50–75)	59.5 (46–73) p=0.001 vs AF
n (rate per 100 pat-y)	179 (1.87)	132 (1.73)	47 (2.4)*
Cerebral	53 (0.55)	42 (0.55)	11 (0.56)
Gastrointestinal	65 (0.68)	51 (0.67)	14 (0.71)
Retroperitoneal	2 (0.02)	1 (0.01)	1 (0.05)
Ocular causing blindness	4 (0.04)	2 (0.03)	2 (0.1)
Blood transfusion ≥2 U	13 (0.13)	7 (0.1)	6 (0.30)
Loss of hemoglobin ≥2 g/dL	33 (0.34)	24 (0.31)	9 (0.46)
Articular bleeding	9 (0.09)	5 (0.06)	4 (0.2)

*VTE versus AF: relative risk, 1.4; 95% confidence interval, 1.02 to 1.85; *P=0.032.*

Poli et al; ***Circulation. 2011;124:824-829***

Efficacy and Harms of Direct Oral Anticoagulants in the Elderly for Stroke Prevention in Atrial Fibrillation and Secondary Prevention of Venous Thromboembolism Systematic Review and Meta-Analysis

- 31,418 elderly participants aged ≥75 years out of a total of 102,479 participants aged ≥18 years.
- Mean age ranged from 64.5 to 71.7 years in AF studies and 54.4 to 59.0 years in VTE studies

Sharma M, ***Circulation. 2015;132:194-204***

Bleeding rates in VTE in the elderly

Major Bleeding	>75 y (12.5% of total VTE pt)		< 75 y	
RCTS	DOACs	VKA	DOACs	VKA
Dabigatran	8/231=3.4%	10/262=3.8%	35/2553=1.37%	46/2554=1.8%
Rivaroxaban	8/655=1.2%	28/624=4.4%	40/4130=0.96%	72/3756=1.9%
Apixaban	4/398=1%	16/370=4.3%	15/2676=0.56%	49/2689=1.8%
Edoxaban (MB+ CRNMB)	70/560=12.5%	82/544=15%	279/3558=7.8%	341/3578=9.5%

Modified from Sharma M, ***Circulation. 2015;132:194-204***

Risk factors for bleeding during anticoagulation: treatment-associated factors

Duration and timing from initiation of treatment

First 3-6 months of therapy

Intensity of anticoagulation

INR values > 4.5

Quality of anticoagulation monitoring

Use of short half-life VKA drug
Poor anticoagulation monitoring

Palareti & Cosmi; ***T&H, 2009***

Treatment-associated risk factors for bleeding First 3-6 months of anticoagulation in VTE

- anticoagulation intensity with initial parenteral therapy may be greater than with VKA therapy
- anticoagulant control less stable
- predispositions to anticoagulant-induced bleeding may be uncovered
- more comorbid conditions: recent surgery, trauma, serious illness.

Kearon et al *ACCP,. 2012*

Risk Factors For Bleeding During Anticoagulation:Person-Dependent Factors

Genetic factors	Co-morbid conditions
Polymorphisms of VKORC1 and CYP2C9	History of major bleeding (especially GI)
Mutation in factor IX propeptide (low factor IX levels)	History of atherosclerotic stroke
Natural conditions	Uncontrolled hypertension
Advanced age	cancer
Women	Congestive heart failure
Personal characteristics/life habits	**Co-medication**
Tendency to falls	Antiplatelet drugs
Insufficient information and education to the treatment	NSAIDs
Poor compliance	Drugs affecting pharmacokinetics or pharmacodynamics of VKAs
Poor dietary intake of vitamin K	
Nutritional supplements and herbal products	
Alcohol abuse	
Absence of familial or social support	

Palareti & Cosmi; *T&H, 2009*

Bleeding Risk in Very Old Patients on Vitamin K Antagonist Treatment: Results of a Prospective Collaborative Study on Elderly Patients Followed by Italian Centres for Anticoagulation (EPICA)

	Risk Factors Associated With Bleeding Events: Competing-Risk Regression Analysis		
	Hazard Ratio	95% CI	*P*
Male sex	1.42	0.98 –2.08	0.06
Age ≥85 y	1.02	0.71–1.47	0.88
VTE vs AF	1.51	1.01–2.27	0.04
Hypertension	1.30	0.83–2.02	0.23
History of bleeding	5.46	3.29–9.05	<0.0001
Renal failure (serum creatinine ≥ 1.5 mg/dL	1.10	0.67–1.79	0.69
Active cancer	2.41	1.47–3.95	<0.0001
History of falls	3.06	1.47–3.95	<0.0001
Comedications (3 drugs)	1.32	1.77–5.27	0.16

Poli et al; ***Circulation. 2011;124:824-829***

Bleeding risk assessment in anticoagulation for VTE

- At the start of treatment:
- comparison/choice of anticoagulant regimens
- identify patients who might benefit from more careful management of anticoagulation

- After 3 months:
- To decide risk/benefit of extended anticoagulation, particularly in unprovoked VTE
- help counsel and inform patients about their potential risk for hemorrhage while on anticoagulants

ACCP 2016 Guidelines: Highlights

Treatment beyond Acute Period

- Surgery-associated proximal or distal DVT/PE: recommend 3 months. (1B)
- Non-surgical transient risk factor: recommend 3 months over 6 or more months. (1B)

- Unprovoked isolated distal/proximal DVT/PE and low/intermediate risk for bleeding: suggest extended anticoagulation (2B). **High bleeding risk: 3 months (1B).**

Kearon C et al. ***CHEST 2016; 149(2):315-352***

Antithrombotic Therapy for VTE Disease

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: ACCP Evidence-Based Clinical Practice Guidelines.

Risk factors for bleeding in anticoagulation (evidence based review in VTE/AF)

- **Age > 65 y**
- **Age >75 y**
- Previous bleeding
- Cancer
- Metastatic cancer
- Renal failure
- Liver failure
- Thrombocytopenia
- Previous stroke
- Diabetes
- Anemia
- Antiplatelet therapy
- Poor anticoagulant control
- Comorbidity and reduced functional capacity
- Recent surgery
- Frequent falls
- Alcohol abuse

Kearon C et al. ***CHEST 2016; 149(2):315-352***

Antithrombotic Therapy for VTE Disease

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: ACCP Evidence-Based ClinicalPractice Guidelines.

	Estimated Absolute Risk of Major Bleeding, %		
Categorization of Risk of Bleeding	**Low risk (0 factors)**	**Moderate risk (1 factor)**	**High risk (≥2 factors)**
Anticoagulation 0-3 mo			
Baseline risk %	**0.6**	**1.2**	**4.8**
Increased risk %	**1.0**	**2.0**	**8.0**
Total risk %	**1.6**	**3.2**	**12.8**
Anticoagulation after first 3 mo			
Baseline risk %	**0.3**	**0.6**	**≥ 2.5**
Increased risk %	**0.5**	**1.0**	**≥ 4.0**
Total risk %	**0.8**	**1.6**	**≥ 6.5**

this categorization scheme has not been validated.

Kearon C et al. ***CHEST 2016; 149(2):315-352***

What makes a good clinical prediction rule for bleeding in patients with VTE (also elderly)?

- targeted at pts with unprovoked VTE after at least 3-6 mo of treatment.
- predictors measured at 3-6 mo, rather than at anticoagulation initiation
- able to discriminate well low/high risk of bleeding
- or
- identify annual risk of major bleeding high enough to consider anticoagulation discontinuation
- bleeding events adjudicated by independent experts blinded to baseline predictors
- updated information on predictors during follow-up (i.e. dynamic prediction) to assess any changes in the absolute risk

Van Es et al, ***Thrombosis Research 152 (2017) 52 –60***

Key elements in deriving and validating a new prediction score or model

- predictor selection
- model development: minimum of 10 outcomes per each predictor
- model performance:c-statistics
- internal validation
- external validation: mandatory.

- Ideally a prospective study performed to evaluate impact of score on patient-important outcomes and healthcare costs

Van Es et al, ***Thrombosis Research 152 (2017) 52 –60***

Clinical prediction scores and models for major bleeding in patients with VTE

Score	Score items (points)	F-up	Performance
Kuijer	**-Age ≥ 60 years (+1.6)** -Female sex (+1.3) -Cancer (+2.2)	3 mo.	Low risk (0 pts): 0.6% Intermediate risk (1.3 –2.9 pts): 1.7% High risk (≥ 3.5 pts): 6.7%
RIETE	-Recent major bleeding (+2) -Creatinine N 1.2 mg/dL (+1.5) -Anemia (+1.5) -Cancer (+1) -Clinically overt PE (+1) **-Age > 75 years (+1)**	3 mo	Low risk (0 pts): 0.1% Intermediate (1 –4 pts): 2.8% High (≥ 4.5 pts): 6.2%
EINSTEIN model (ISTH criteria for MB)	-Rivaroxaban (vs. VKA) **-Age (continuous)** -Hemoglobin (continuous) -Male sex if hemoglobin ≥ 12 g/dL -Hemoglobin if male (continuous) -Black (vs. Caucasian) -Asian (vs. Caucasian) -History of cardiovasculardisease	3, 6, 12 mo	Crude c-statistic: 0.74 Adjusted c-statistic: 0.68

Van Es et al, ***Thrombosis Research 152 (2017) 52 –60***
Modified

Clinical prediction scores and models for major bleeding in patients with VTE

Score	Score items (points)	F-up	Performance
Hokusai model (ISTH criteria for MB)	-Female sex (+1) -Concomitant (+1) antiplatelet therapy -Hemoglobin ≤ 10 g/dL (+1) -History of hypertension (+1) -Systolic blood pressure N 160 mm Hg (+1)	3, 6, 12 mo	Crude c-statistic: 0.71 Adjusted c-statistic: 0.62
VTE-BLEED (ISTH criteria for MB)	-Active cancer (+2) -Male patient with uncontrolled hypertension (+1) -Anemia (+1.5) -History of bleeding (+1.5) -Creatinine clearance 30 –60 mL/min (+1.5) **-Age ≥ 60 years (+1.5)**	6 mo	Dabigatran: between 30 d. and 6 m -Crude c-statistic: 0.75 -Low risk (0 –1.5 pts): 0.2% -High risk (≥ 2 pts): 1.4% -OR high v low: 6.5 Warfarin: between 30 d and 6 mo -Crude c-statistic: 0.78 -Low risk (0 –1.5 pts): 0.4% -High risk (≥ 2 pts): 2.8% -OR high v low: 6.5

Van Es et al, ***Thrombosis Research 152 (2017) 52 –60***
Modified

Prospective, multicenter validation of prediction scores for major bleeding in elderly patients with venous thromboembolism.

prospective multicenter Swiss cohort study,
663 patients aged > 65 years with acute VTE
Follow-up 90 days, major bleeding: 4.2%

Table 3 Accuracy for high- vs. intermediate-/low-risk categories to predict a first major bleeding at 90 days

	Sensitivity,% (95% CI)	Specificity,% (95% CI)	Positive PV,% (95% CI)	Negative PV,% (95% CI)	Positive LHR (95% CI)	Negative LHR (95% CI)	Goodness-of-fit*
OBRI	7.1 (2.0–22.6)	92.9 (90.6–94.7)	4.3 (1.2–14.2)	95.8 (93.9–97.1)	1.01 (0.26–3.95)	1.00 (0.90–1.11)	0.82
Kuijer score	10.7 (3.7–27.2)	85.2 (82.2–87.7)	3.1 (1.1–8.7)	95.6 (93.6–97.0)	0.72 (0.24–2.14)	1.05 (0.92–1.20)	0.84
Kearon score	21.4 (10.2–39.5)	82.8 (79.7–85.6)	5.2 (2.4–10.9)	96.0 (94.0–97.3)	1.25 (0.60–2.59)	0.95 (0.78–1.15)	0.53
RIETE score	14.3 (5.7–31.5)	91.0 (88.5–93.0)	6.6 (2.6–15.7)	96.0 (94.1–97.3)	1.59 (0.62–4.08)	0.94 (0.81–1.10)	0.87

CI, confidence interval; OBRI, Outpatient Bleeding Risk Index; PV, predictive value; LHR, likelihood ratio. **P*-values from Pearson's chi-square goodness-of-fit test. *P*-values ≥ 0.05 indicate an adequate goodness-of-fit.

Scherz N et al, ***JTH 2013, 11:435-43***

The predictive ability of bleeding risk stratification models in very old patients on VKA treatment for venous thromboembolism.

	Low number (ratex100pt/yr)	**Intermediate** number (ratex100pt/yrs)	**High** number (ratex100pt/yrs)	RR (95% CI)	**p**	**C statistics**
Beyth et al (OBRI)	NA	39/841 (2.6)	2/33 (2.6)	1.0 (0.25-8.3)	0.9	0.58-0.51
Gage et al (HEMORR2HAGES	8/210 (2.1)	26/611 (2.3)	7/50 (6.9)	3.0 (1.1-6.9)	0.01 (*)	0.60
Ruiz Lopez et al (RIETE)	NA	40/876 (2.5)	1/8 (5.9)	2.35 (1.5-4.0)	0.0001	0.61-0.51
Pisters et al (HAS-BLED)	17/473 (1.9)	NA	23/400 (3.4)	1.6 (0.8-3.1)	0.1	0.55-0.58
Fang et al (ATRIA)	25/644 (2.2)	1/9 (4.5)	6/62 (1.1)	0.3 (0.1-1.0)	0.03	0.58-0.56
ACCP 2012	NA	9/229 (2.0)	21/643 (2.7)	1.2 (0.7-2.9)	0.6	0.55-0.52

Poli et al; ***Thromb Haemost 2013; 11 : 1053–8***

Derivation and validation of a novel bleeding risk score for elderly patients with venous thromboembolism on extended anticoagulation.

- prospective multicenter cohort study in VKA extended anticoagulation
- 743 pts ≥65 y with VTE
- time to first major bleed up to 36 mo.
- 66 (9%) pts with major bleeding.
- Clinical score : previous bleeding, active cancer, low physical activity, anemia, thrombocytopenia, antiplatelet drugs/NSAIDs, and poor INR control
- 1.4 events in low-risk, 5.0 events in moderate-risk, and 12.2 events per 100 patient-years in high-risk patients.
- c-statistic: 0.78 at 3 mo and 0.71 at 36 mo.
- External validation needed

Seiler at al; ***Thromb Haemost. 2017;117(10)***

Limitations of available clinical prediction scores for bleeding risk

- decisions about treatment duration left to the discretion of the physician, with potential risk of indication bias.
- more likely anticoagulation stopped in pts with highest risk of bleeding, affecting the discriminatory performance as well as positive predictive value
- mainly derived in inception cohorts of patients with provoked or unprovoked VTE who started anticoagulant therapy, rather than in patients with unprovoked VTE who had been treated for at least 3 months
- the predictive value of variables measured at baseline may be different after the first 3 months of treatment

Van Es et al, ***Thrombosis Research 152 (2017) 52 –60***

Limitations of available clinical prediction scores for bleeding risk

- modifiable conditions at baseline, such as anemia, acute renal insufficiency, and uncontrolled hypertension may be not predictive after the initial period
- Active cancer not useful as a predictor in unprovoked VTE
- risk factors unavailable at the start of treatment and/or transient and unpredictable:
- surgery, invasive or vascular procedures,trauma
- drug–drug or food–drug interactions; aspirin, NSAIDS
- a single risk factor, when severe, will result in a high risk of bleeding (eg, major surgery within the past 2 d, severe thrombocytopenia)
- In VTE, incidence of bleeding low in RCTs, short follow-up

Conclusions

- No solid external validation studies of clinical prediction scores
- None are useful to assess risk of bleeding and guide duration of treatment for the elderly.
- risk factors can still be useful to identify patients at higher risk of bleeding.
- Older age, renal impairment, and a history of bleeding are consistent and well-established and overlap in many scores
- Prescribing DOACs at a prophylactic dose or alternative drugs could be an option in subjects at a high risk of bleeding but more studies are needed in this setting.

Issues for future research on bleeding scores in anticoagulation for VTE in the elderly

- bleeding risk scores in cohorts of elderly pts with VTE with an extended follow-up (no validated CPR available)
- uniform criteria for major bleeding
- blinded outcome assessment
- evaluation of risk factors for ICH/ fatal bleeding
- bleeding risk factors with new anticoagulants
- trials evaluating the impact of the scores on patient outcomes
- Use of biomarkers (eg growth differentiation factor (GDF)-15, high-sensitivity cardiac troponin T)