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ORIGINAL ARTICLE

The predictive ability of bleeding risk stratification models in very old patients on vitamin K antagonist treatment for venous thromboembolism: results of the prospective collaborative EPICA study

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Summary. *Background:* The optimal duration of anticoagulant treatment after venous thromboembolism (VTE) should be evaluated in relation to bleeding risk. This assessment is particularly difficult with elderly patients, because of their increased risk of both recurrences and hemorrhages. Bleeding risk stratification models have been proposed, but their predictive ability in very elderly patients is unknown. We aimed to assess six bleeding stratification models in this setting, by using information available in our dataset. *Patients and methods:* Patients aged $\geq$ 80 years receiving vitamin K antagonists (VKAs) for the secondary prevention of VTE were eligible for this prospective cohort study. All patients were followed at Italian anticoagulation clinics for monitoring of VKA treatment. Risk factors for bleeding were collected, and major bleeding events and mortality were documented during follow-up. The association of bleeding events with the available risk factors was tested by means of Cox regression analysis; the *c*-statistic was used to quantify the predictive validity of the classification schemes. *Results:* A total of 1078 patients (37.2% males; mean age, 84 years) were enrolled in the study, for a total observation period of 1981 patient-years. The rate of major bleeding was 2.4 per 100 patient-years (47 events; one was fatal). The mortality rate was 5.2 per 100 patient-years. None of the considered risk factors were significantly associated with bleeding events. The predictive validity of the risk stratification models was low, and the most accurate model was not specifically developed for VTE patients ($HEMORR_2HAGES$, *c*-statistic 0.60, 95% confidence interval 0.49–0.70). *Conclusions:* Bleeding risk stratification models appear to have little accuracy in very elderly VTE patients.

Keywords: bleeding, bleeding scores, elderly, venous thromboembolism, vitamin K antagonist.

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Introduction

Patients with venous thromboembolism (VTE) are at considerable risk of long-term recurrences. Prospective cohort studies have found an overall cumulative incidence of recurrent VTE of ~ 17% after 2 years and of up to ~ 30% after 8–10 years [1,2]. This risk of recurrence varies according to the presence and type of major provoking factors, and is generally expected to be low if the event was associated with transient risk factors [3], high if the event was apparently unprovoked [4], and very high if the event occurred in association with cancer [5]. On the basis of this risk categorization, current guidelines recommend the administration of anticoagulant treatment for the secondary prevention of a first episode of VTE for 3 months to all patients, and the extension of this treatment indefinitely in patients with cancer and in patients with unprovoked VTE and a low to moderate bleeding risk [6]. The assessment of the risk/

benefit ratio of anticoagulant treatment is particularly important in fragile populations, such as very elderly patients. To assist clinicians with the evaluation of the individual risk of bleeding, the American College of Chest Physicians (ACCP) guidelines have proposed a specific risk score aimed at categorizing patients into three risk groups: low, moderate, and high [6]. This risk score, as well as other stratification models proposed for patients on anticoagulant therapy, is potentially useful, but its predictive accuracy may vary among different patient populations. For this reason, we aimed to assess the predictive accuracy of risk stratification models, including the ACCP risk score, in a large population of very elderly patients with VTE.

Methods

Twenty-seven centers affiliated to the Italian Federation of Anticoagulation Clinics participated in the EPICA Study, which prospectively followed 4093 very elderly patients who started vitamin K antagonist (VKA) treatment after the age of 80 years for either atrial fibrillation (AF) or VTE. The study was aimed at evaluating the risk of bleeding and thrombosis during anticoagulant treatment in the elderly. The setting and the overall results of the study have been previously described [7].

For the purpose of this substudy, we considered the 1078 patients who were treated for the secondary prevention of VTE. Briefly, patients were followed up by periodic International Normalized Ratio (INR) measurements, and maintained at an intended therapeutic range of 2.0–3.0 by the centers. The centers establish the date for the subsequent visits, prescribe the daily VKA dosages, and monitor and record changes in patient habits, diet, comedications, and the occurrence of concomitant illnesses, bleeding, and thrombotic complications, on the basis of patient interviews.

The quality of anticoagulation was calculated as time in therapeutic range (TTR), with the linear interpolation method of Rosendaal *et al.* [8]. This calculation was started at the beginning of treatment.

Bleeding risk stratification models

We classified our patients for bleeding risk by using previously published risk stratification models: OBRI index [9], $HEMORR_2HAGES$ [10], RIETE score [11], HASBLED [12], ATRIA score [13], and ACCP 2012 [6] (Table 1). We classified patients into the appropriate strata of each scheme by using available baseline clinical characteristics: age, previous stroke or transient ischemic attack, hypertension (defined as any hypertension), history of bleeding, diabetes, cancer, active cancer, renal failure, history of falls, antiplatelet drugs use, comedications (three or more drugs), and TTR of < 60%. When the score included other items not accessible in our dataset, the calculation was performed by including only available data. In particular, no information was available on CYP2C9 single-nucleotide polymorphisms, ethanol abuse, and platelet count.

Follow-up and endpoints

Follow-up visits were scheduled every 2–4 weeks for INR monitoring. Patients who missed check-ups for more than 2 months were contacted (personally or through their family or general practitioner), and the reason for interrupting treatment monitoring was recorded. In the case of death, further information about its cause was requested. Deaths for all causes were recorded.

The endpoint of the study was the occurrence of major bleeding. A bleeding event was defined as major when it was fatal, intracranial (documented by imaging), ocular causing blindness, articular, or retroperitoneal; or when surgery or invasive maneuvers were necessary to stop bleeding; or when transfusion of more than two blood units was required; or when the hemoglobin level was reduced by > 2 g dL^{-1}.

Statistical analysis

Incidence rates for major bleeding events were calculated as the number of events per 100 patient-years of observation [14]. For this calculation, observation started at the beginning of follow-up and ended when patients died, stopped treatment for any reason, or experienced a major bleeding event. The SPSS statistical software package, version 19 for Windows (SPSS, Chicago, IL, USA) was used for data processing. Data are expressed as median and range, owing to their skewed distribution. Statistical analysis was performed with Fisher's exact test (categorical data), and $P < 0.05$ was chosen for statistical significance. To ascertain whether there was an association of bleeding events with the risk factors considered by the commonly used risk stratification models for bleeding risk, we performed a Cox regression analysis. All variables included in the analysis were collected at baseline. The *c*-statistic, a measure of the area under the receiver operating characteristic curve, quantified the predictive validity of the classification schemes and tested the hypothesis that this classification schemes performed significantly better than chance; $P < 0.05$ was chosen for statistical significance (Harrell's method) [15].

Results

We prospectively followed up 1078 patients (401 males, 37.2%) who started VKA treatment at the age of 80 years or older for the secondary prevention of VTE. The total observation period was 1981 patient-years, and the median age of the patients at the time of inclusion was 84 years (range, 80–98 years). The clinical characteristics of the whole population are reported in Table 2.

Table 1 Bleeding risk stratification models

Models	Population design	Calculation of risk score	Low risk	Moderate risk	High risk
OBRI Beyth *et al.* [9]	Prospective inception cohort	Age ≥ 65 years, previous stroke, GI bleeding in the last 2 weeks, ≥ 1 of recent MI, hematocrit < 30%, creatinine > 1.5 mg dL−1, or diabetes mellitus *1 point for each risk factor*	0	1–2	≥ 3
$HEMORR_2HAGES$ Gage *et al.* [10]	Retrospective analysis of NRAF cohort	Hepatic or renal disease, ethanol abuse, malignancy, age > 75 years, reduced platelet count, rebleeding risk, uncontrolled hypertension, anemia, genetic factors (CYP2C9 single-nucleotide polymorphisms), excessive fall risk, previous stroke/TIA *1 point for each risk factor present, and 2 points for previous bleed*	0–1	2–3	≥ 4
RIETE score Ruíz-Giménez *et al.* [11]	Prospective inception cohort	Recent major bleeding, creatinine levels > 1.2 mg dL−1, anemia, cancer, clinically overt PE, age > 75 years *1 point for each risk factor present, 1.5 points each for creatinine and anemia, 2 points for previous bleed*	0	1–4	> 4
HAS-BLED Pisters *et al.* [12]	Retrospective analysis of Euro Heart Survey cohort	Hypertension, abnormal renal and/or liver function, stroke, bleeding history, labile INR, elderly (age > 65 years), drugs (antiplatelets/NSAIDs)/concomitant alcohol (≥ 8 units per week) *1 point for each risk factor*	0–2	NA	≥ 3
ATRIA score Fang *et al.* [13]	Retrospective analysis of the ATRIA cohort	Anemia, severe renal disease (GFR < 30 mL min−1 or dialysis-dependent), age ≥ 75 years, previous bleed, hypertension 1 point each for the presence of previous bleed and hypertension, *2 points for age ≥ 75 years, and 3 points each for the presence of anemia and renal disease*	0–3	4	5–10
ACCP Kearon *et al.* [6]		Age > 65 years, age > 75 years, 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 *1 point for each risk factor*	0–1	NA	≥ 2

GFR, glomerular filtration rate; GI, gastrointestinal; INR, International Normalized Ratio; MI, myocardial infarction; NA, not available; NSAID, non-steroidal anti-inflammatory drug; PE, pulmonary embolism; TIA, transient ischemic attack.

During follow-up, 103 patients died (total mortality rate, 5.2 per 100 patient-years). The causes of mortality were fatal bleeding in one patient, cardiovascular disease in 34 patients, ischemic stroke in two patients, cancer in 21 patients, and sudden death with no additional information in 12 patients. The remaining 33 patients died from different causes that were not related to VKA treatment. The quality of anticoagulation, expressed as TTR, was 59.5% (interquartile range 43–73).

Bleeding events

During the whole observation period, 47 major bleeds were recorded (rate 2.4 per 100 patient-years), and 11 were cerebral (0.56 per 100 patient-years). During the first 3 months of treatment, we recorded eight major bleeds (2.97 per 100 patient-years). No difference was found in TTR between patients with or without bleeding events ($P = 1.0$). The results of the univariate Cox regression analysis for bleeding risk are reported in Table 3. None of the considered parameters were significantly associated with bleeding events.

When we applied the considered bleeding risk stratification models to our cohort, we found that all models were scarcely associated with bleeding risk, with the exception of the high-risk group identified by the $HEMORR_2HAGES$ score (Table 4). Finally, analysis of the *c*-statistic confirmed the modest predictive value of all models (Table 5).

Discussion

In this large cohort of very elderly patients treated with VKAs for the secondary prevention of VTE, none of the

Table 2 Clinical characteristics of patients in relation to the indication for vitamin K antagonist (VKA) treatment

	VTE
N	1078
Males, *n* (%)	401 (37.2)
Median age in years (IQR)	84 (80–98)
Follow-up period (patient-years)	1981
Mean follow-up period in years (SD)	1.83 (1.9)
Past medical history, no. (%)	
Heart failure	105 (10.3)
Hypertension	652 (62.9)
Diabetes	137 (13.4)
Coronary artery disease/peripheral artery disease	163 (16.1)
Cancer	110 (10.1)
Previous stroke/TIA	108 (10.3)
Serum creatinine $\geq$ 1.5 mg dL−1	85 (9.6)
Antiplatelet drugs	52 (5.1)
No. of drugs associated ($\geq$ 3)	507 (49.7)
Time in therapeutic range (IQR)	59.5 (46–73)

IQR, interquartile range; SD, standard deviation; TIA, transient ischemic attack. Data available for 887 patients.

Table 3 Risk factors associated with bleeding events: univariate analysis

	Bleeds *n* (%)	No bleeds *n* (%)	HR	95% CI	*P*-value
Previous TIA/ stroke	4 (8.5)	104 (10.1)	0.8	0.3–2.2	0.7
Hypertension	34 (72)	118 (62.5)	1.5	0.8–2.8	0.2
History of bleeding	3 (6.4)	25 (2.5)	2.0	0.6–6.4	0.2
Renal failure (serum creatinine $\geq$ 1.5 mg dL−1)	6 (14.6)	78 (9.2)	1.8	0.7–4.2	0.2
TTR	23 (50)	510 (50)	1.2	0.6–2.1	0.6
Cancer	11 (23.9)	182 (18.5)	1.1	0.6–2.3	0.7
Active cancer	9 (19.6)	103 (10.5)	1.6	0.7–3.3	0.2
Antiplatelet use	1 (2.2)	51 (5.2)	0.4	0.05–2.8	0.3
History of falls	5 (11.1)	60 (6.3)	2.0	0.7–5.0	0.1
Comedications (three or more drugs)	30 (65.2)	475 (48.8)	1.7	0.9–3.0	0.1
Diabetes mellitus	8 (17.0)	129 (13.0)	1.5	0.7–3.2	0.3

CI, confidence interval; HR, hazard ratio; TIA, transient ischemic attack; TTR, time in therapeutic range.

proposed risk stratification models were sufficiently accurate for the prediction of bleeding risk. In addition, none of the individual variables collected was significantly associated with the occurrence of bleeding.

Elderly patients with VTE are at increased risk of both recurrences and bleeding complications, and the decision on the optimal duration of secondary prevention with VKAs is therefore particularly difficult. In the RIETE registry, patients aged $\geq$ 80 years had a 1.7-fold increased risk of major bleeding events as compared with patients younger than 80 years (3.4% and 2.1%, respectively), and a two-fold increased risk of fatal bleeding (0.8% and 0.4%, respectively) [16], although the incidence of fatal pulmonary embolism was also increased, and was higher than that of fatal bleeding, suggesting that advanced age as such should not prevent elderly patients from receiving an adequate duration of secondary prevention with anticoagulant drugs. An extended treatment duration after the first 3 months is not only recommended for patients with unprovoked VTE, but may also be considered for patients with non-surgical risk factors if the risk of bleeding is low [6]. In the MASTER registry, severe medical diseases and immobilization were significantly more common in patients aged $\geq$ 80 years than in any other age group [17]. Although these risk factors are usually classified as transient, their resolution in very elderly patients is commonly incomplete, thus suggesting the need for extended treatment. Thus, the availability of accurate bleeding risk prediction models would be particularly important in this setting to drive difficult treatment decisions. Unfortunately, on the basis of the results of our study, none of the available models seems to be able to identify elderly patients with VTE at high risk of bleeding. Likewise, we were unable to propose a specific risk stratification model for our patients, given that none of the individual variables was significantly associated with bleeding risk after univariate analysis. In this analysis, only a history of falls and the presence of comedications resulted in a nearly significant association, with odds ratios of 2.0 and 1.7, respectively, and a *P*-value of 0.10.

It should be noted that only two of the bleeding risk prediction models tested in our study have been proposed for or developed in VTE patients [6,11], the others having been studied in AF patients only. However, we decided to verify the applicability of all of these models to VTE patients, considering their widespread use. When we evaluated the predictive ability of the different schemes, in all models the confidence intervals of the *c*-statistics overlapped, suggesting that none of the tested models is sufficiently accurate in predicting bleeding risk in this population.

Because age is a bleeding risk factor included in all models, it is possible that the application of all of these scores to a very old cohort limits their predictive ability. In this study, only the ATRIA and RIETE scores [11,13] were associated with a significantly increased risk of bleeding in patients classified as being at high risk as compared with patients classified as being at lower risk. Unfortunately, the high-risk group of the RIETE score included a very limited number of patients, suggesting low clinical applicability of this model.

This study has a number of limitations that need to be acknowledged. No adjudication panel was planned for the study, so we accepted as major bleeding or death all events indicated by each participating center. However, participating centers were required to clearly describe all adverse events, and, for all events that lacked an adequate description in the dataset, the coordinating center requested further information to ascertain the real occurrence of the event. When the event did not meet the defi-

Table 4 Rate of hemorrhage in relation to bleeding risk stratification models and categorization of bleeding risk

Reference	Low number (rate per 100 patient-years)	Intermediate number (rate per 100 patient-years)	High number (rate per 100 patient-years)	RR (95% CI)	*P*-value
Beyth *et al.* [9]	NA	39/841 (2.6)	2/33 (2.6)	1.0 (0.25–8.3)	0.9
Gage *et al.* [10]	8/210 (2.1)	26/611 (2.3)	7/50 (6.9)	3.0 (1.1–6.9)	0.01*
Ruíz-Giménez *et al.* [11]	NA	40/876 (2.5)	1/8 (5.9)	2.35 (1.5–4.0)	0.0001
Pisters *et al.* [12]	17/473 (1.9)	NA	23/400 (3.4)	1.6 (0.8–3.1)	0.1
Fang *et al.* [13]	25/644 (2.2)	1/9 (4.5)	6/62 (1.1)	0.3 (0.1–1.0)	0.03
ACCP [6]	NA	9/229 (2.0)	21/643 (2.7)	1.2 (0.7–2.9)	0.6

ACCP, American College of Chest Physicians; NA, not available; CI, confidence interval; RR, relative risk.
*Low and intermediate vs. high risk.

Table 5 Predictive ability of the bleeding risk stratification models

	Predictive ability			
	Continuous variables		Categorized variables	
Reference	*c*-statistic (95% CI)	*P*-value	*c*-statistic (95% CI)	*P*-value
Beyth *et al.* [9]	0.58 (0.49–0.67)	0.07	0.51 (0.41–0.62)	0.8
Gage *et al.* [10]	0.60 (0.50–0.70)	0.03	0.60 (0.49–0.70)	0.06
Ruíz-Giménez *et al.* [11]	0.61 (0.51–0.71)	0.02	0.51 (0.41–0.62)	0.8
Pisters *et al.* [12]	0.55 (0.46–0.64)	0.27	0.58 (0.48–0.68)	0.1
Fang *et al.* [13]	0.58 (0.48–0.67)	0.1	0.56 (0.45–0.67)	0.2
ACCP [6]	0.55 (0.45–0.64)	0.29	0.52 (0.42–0.62)	0.6

CI, confidence interval.

nition, it was not included. In relation to the application of bleeding risk models, we used available parameters. The dataset of the study lacked information about: liver function, anemia, alcohol consumption, and genetic factors (CYP2C9 single-nucleotide polymorphisms). However, the patients enrolled were all very old outpatients, who were selected because they were eligible for anticoagulant treatment; thus, patients judged to be too frail for treatment and younger patients were probably excluded. In addition, genetic testing for warfarin treatment was recently considered to be not relevant for treatment [6]. Our cohort had a long follow-up, and the bleeding risk associated with the induction phase will probably not play a key role in the whole bleeding risk recorded.

Finally, we acknowledge that the original bleeding risk clinical prediction rules (CPRs) were derived and validated in different settings (primary care and non-anticoagulation clinic populations) and with different indications for anticoagulation – some included a wider mix of indications (more heterogeneous samples). It may be that the differences in these characteristics have influenced the results, along with the different criteria for major bleeding and length of follow-up of the different studies. The accuracy of the different CPRs could not be adjusted for our study disease prevalence according to Bayes' theorem, because we did not have access to the original data for the calculation of each score likelihood ratio [18].

In conclusion, none of the available bleeding stratification models appears to have sufficient predictive ability in a large population of VTE patients aged $\geq$ 80 years treated with VKAs. Future studies are needed to improve the risk/benefit assessment of anticoagulant therapies in this setting.

Addendum

D. Poli: conception and design of the study, acquisition, analysis and interpretation of data, and drafting and revision of the paper; E. Antonucci: acquisition, analysis and interpretation of data, and drafting and revision of the paper; S. Testa: acquisition of data, and revision of the paper; B. Cosmi: conception and design of the study, interpretation of data, and drafting and revision of the paper; G. Palareti: revision of the intellectual content of the paper; W. Ageno: conception and design of the study, interpretation of data, and drafting and revision of the paper.

Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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