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Comparison of bleeding risk scores in elderly patients receiving extended anticoagulation with vitamin K antagonists for venous thromboembolism

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ABSTRACT

Background: In elderly patients with venous thromboembolism (VTE), the decision to extend anticoagulation beyond 3 months must be weighed against the bleeding risk. We compared the predictive performance of 10 clinical bleeding scores (VTE-BLEED, Seiler, Kuijer, Kearon, RIETE, ACCP, OBRI, HEMORR$_2$HAGES, HAS-BLED, ATRIA) in elderly patients receiving extended anticoagulation for VTE.

Methods: In a multicenter Swiss cohort study, we analyzed 743 patients aged ≥65 years who received extended treatment with vitamin K antagonists after VTE. The outcomes were the time to a first major and clinically relevant bleeding. For each score, we classified patients into 2 bleeding risk categories (low/moderate vs. high). We calculated likelihood ratios and the area under the receiver operating characteristic (ROC) curve for each score.

Results: Over a median anticoagulation duration of 10.1 months, 45 patients (6.1%) had a first major and 127 (17.1%) a clinically relevant bleeding. The positive likelihood ratios for predicting major bleeding ranged from 0.69 (OBRI) to 2.56 (Seiler) and from 1.07 (ACCP) to 2.36 (Seiler) for clinically relevant bleeding. The area under the ROC curves were poor to fair and varied between 0.47 (OBRI) and 0.70 (Seiler) for major and between 0.52 (OBRI) and 0.67 (HEMORR$_2$HAGES) for clinically relevant bleeding.

Conclusions: The predictive performance of most clinical bleeding risk scores does not appear to be sufficiently high to identify elderly patients with VTE who are at high risk of bleeding and who may therefore not be suitable candidates for extended anticoagulation.

KEY WORDS: anticoagulants, bleeding, elderly, risk scores, venous thromboembolism

WHAT IS KNOWN ABOUT THIS TOPIC?

- Elderly patients represent the majority of cases of venous thromboembolism, and have a higher risk of bleeding during anticoagulant treatment compared to younger patients.
- The benefits of extended anticoagulation (> 3 months) after acute venous thromboembolism must be carefully weighed against its risks.
- The predictive performance of bleeding risk scores during extended anticoagulation in elderly patients is uncertain.

WHAT DOES THIS PAPER ADD?

- We compared the predictive performance of 10 bleeding risk scores in 743 elderly patients with venous thromboembolism in a multicenter Swiss cohort study. The discriminative power of the scores varied between poor to fair.
- The predictive performance of most bleeding risk scores appears to be insufficient to accurately identify elderly patients with venous thromboembolism who are at high risk of bleeding and are no suitable candidates for extended anticoagulation.
- Given the clinical complexity of multimorbid, polymedicalized elderly patients, it is possible that a clinical model-based bleeding risk stratification is doomed to failure, and future research should focus on the validation of elderly-friendly anticoagulation strategies.

BACKGROUND

Most patients with acute venous thromboembolism (VTE) should receive at least 3 months of anticoagulant treatment (1). However, whether anticoagulation should be extended beyond the initial 3 months is less clear (1). Although patients anticoagulated with vitamin K antagonists (VKAs) carry a lower risk of bleeding after the initial 3 months of treatment, the risk of major bleeding during extended anticoagulation is still considerable (2.74 events per 100 patient-years), with a case-fatality rate of 9.1% (2). Thus, the benefits of extended treatment must be carefully weighed against its risks. Given that the bleeding risk rises with age (3, 4), this is particularly true for the elderly.

The estimation of the bleeding risk under anticoagulant treatment is complex, as the propensity to bleed is influenced by multiple intercurrent and permanent patient and treatment factors (5). To facilitate physician decision-making, several clinical scores have been derived and validated to predict the short- or longer-term risk of anticoagulation-related bleeding in patients with acute VTE or other diseases (1, 6-14). However, with the exception of the VTE-BLEED and Seiler scores (6, 7), which were derived to predict bleeding occurring after the period of the first 1-3 months of anticoagulant therapy, most scores either focused on the initial 3 months (8, 10) or the entire anticoagulation period (12-15).

Elderly patients do not only represent the majority of cases of VTE (16), they also have a 2-fold increased risk of major and clinically relevant non-major bleeds compared to younger patients (3, 4). Therefore, we aimed to compare the predictive performance of commonly cited bleeding risk scores for VTE and other conditions during extended anticoagulant therapy with VKAs in elderly patients with VTE. We focused on the question whether the scores accurately identify elderly patients at high risk of bleeding who may not be ideal candidates for extended anticoagulation.

METHODS

Study population

We used data from the prospective multicenter SWIss venous Thromboembolism COhort study 65+ (SWITCO 65+), which enrolled in- and outpatients aged ≥65 years with acute, symptomatic, objectively confirmed VTE from nine Swiss university and non-university hospitals between September 2009 and December 2013. Exclusion criteria were inability to provide informed consent (i.e., severe dementia), conditions incompatible with follow-up (i.e., terminal illness or place of living too far away from the study center), insufficient German or French-speaking ability, thrombosis at a different site than the lower limb, catheter-related thrombosis, or previous enrollment in the cohort. The study was approved by the ethics committee at each participating center. The study methods have been published previously in full detail (17).

As we aimed to assess the predictive performance of the bleeding risk scores during extended anticoagulant therapy, our analysis was restricted to patients who continued oral anticoagulation with VKAs beyond the first 3 months after the index VTE. As several scores included variables related to the quality of anticoagulation, we excluded patients who had less than two international normalized ratio (INR) measurements after initiation of anticoagulant therapy. None of the study participants were treated with direct oral anticoagulants, as these agents have not been approved for treatment of VTE in Switzerland during the study recruitment period.

Baseline data collection

Using standardized data collection forms, trained study nurses prospectively collected baseline demographic information (age, sex, weight), history findings (prior bleeding events, physical activity level, risk of falls, alcohol consumption), comorbid

conditions (cancer, cardiorespiratory diseases, diabetes mellitus, chronic liver and renal disease), physical examination (blood pressure) and laboratory findings (hemoglobin, platelet count, creatinine), concomitant antiplatelet therapy, and VTE-related treatments. In patients who gave their consent, an additional blood sample was stored for analysis of genetic risk factors that may influence the risk of bleeding (i.e., presence of CYP2C9 variants).

Risk assessment scores

Using baseline on demographics and clinical data obtained by chart review, we determined the presence of the prognostic variables comprising bleeding risk scores validated for VTE (VTE-BLEED, Seiler, Kuijer, Kearon, RIETE and ACCP score) or other diseases, predominantly atrial fibrillation (Outpatient Bleeding Risk Index [OBRI], HAS-BLED, HEMORR$_2$HAGES, and ATRIA score) (6-14, 18). Based on the prognostic variables, we calculated the 10 prognostic scores and classified each patient in the low- and high-risk (VTE-BLEED) or in the low-, intermediate-, or high-risk category (all other scores; Appendix Table). To ensure comparability, 3-level scores were further dichotomized as lower (low- or moderate risk) vs. high risk. As done in the original derivation studies, the scores were generally calculated using patient data at the time of the index VTE. Exceptions were the variables with regard to poor anticoagulation/INR control (Seiler, ACCP, and HAS-BLED) and the Seiler score variable “previous major bleeding”, which were assessed at the end of the initial 3 months of anticoagulant therapy.

Missing values and score variables not documented in our database (peptic ulcer disease) were assumed to be normal. The hematocrit was calculated by multiplying the hemoglobin level in g/l by 0.3 (19). Whenever possible, we used the exact variable definition as per the original derivation study. When the definition was

not specified or differed from the data available in our database, we used standardized proxy definitions (e.g., platelet count <150 G/l for thrombocytopenia). For instance, we defined “active cancer” or “malignancy” as the presence of a solid or hematologic cancer under chemotherapy, radiotherapy, surgery, and/or palliative care during the 3 months prior to the index VTE. A “history of bleeding”, “previous (major) bleeding”, “recent major bleeding”, “any prior hemorrhage diagnosis”, or “re-bleeding risk” was defined as a bleeding that led to a hospital stay or transfusion. We defined a “history of stroke”, “prior or previous stroke”, or “stroke” as a history of ischemic/hemorrhagic stroke or a transient ischemic attack. An “excessive fall risk” or “frequent falls” were defined as at least 1 fall during the past year or problems with gait, balance, or mobility (20). We defined alcohol abuse as the consumption of >8 units of alcoholic drinks per week (12). Finally, poor anticoagulation/INR control was defined as a time in the therapeutic range (INR 2.0-3.0) of less than 60% based on the Rosendaal method (ACCP, HAS-BLED) or as fewer than 30% of measured INR values in the therapeutic range during the first 3 months of anticoagulation (Seiler) (7, 21).

Study outcomes

Our primary study outcome was the time to a first major bleeding during extended anticoagulation (i.e., after 3 months) up to 36 months of follow-up. We defined major bleeding as fatal bleeding, symptomatic bleeding in a critical area (intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, intramuscular with compartment syndrome), or bleeding resulting in a drop of the hemoglobin level of ≥20 g/l or leading to transfusion of ≥2 units of red blood cells (22). The secondary outcome was the time to a first clinically relevant bleeding, defined as the combined outcome of major or clinically relevant non-major bleeding,

during extended anticoagulation. Clinically relevant non-major bleeding was defined as any bleeding not meeting the definition criteria of major bleeding but requiring medical attention, for instance, a physician consultation or a visit at the emergency department (17, 23).

The outcomes were assessed alternating between face-to-face evaluations and telephone calls after 3 and 6 months and then semi-annually. During each contact, study nurses interviewed patients to obtain information about any bleeding events. In case of a bleeding event or death, medical chart review and interviews of the primary care physicians and family members were performed. The cause of death was evaluated and adjudicated by a committee of 3 blinded clinical experts. Death was considered bleeding-related if it succeeded an intracranial hemorrhage or a bleeding episode leading to hemodynamic instability (24). Final classification was made on the basis of the full consensus of this committee.

Statistical analysis

We compared baseline characteristics of patients with and without major bleeding using chi-square tests for categorical variables and non-parametric rank tests for continuous variables. We calculated the incidence rates of a first major and clinically relevant bleeding and estimated the cumulative bleeding incidence using Kaplan-Meier analysis. We described the proportions of patients classified as lower (low or moderate) vs. high risk of bleeding for each score, and the major and the clinically relevant bleeding rates during extended anticoagulation only (censoring after interruption of the initially prescribed anticoagulation therapy for more than 2 weeks). To evaluate the accuracy of the scores to predict bleeding events, we calculated their positive and negative likelihood ratios (LHRs) for lower- vs. high-risk patients. The discriminative power was assessed by calculating the area under the

receiver operating characteristic (ROC) curve, performing a non-parametric test of the equality of the areas under the curves. We determined the calibration in a logistic regression model using the Pearson chi-square test.

We estimated the potential clinical impact of the risk scores by computing the percentage of potentially avoided first major bleedings vs. the percentage of patients left unnecessarily at risk of recurrent VTE if lower-risk patients were to receive and high-risk patients were not to receive extended anticoagulant treatment. We calculated the unweighted benefit (% of avoided first major bleeds minus % of patients left at risk of VTE recurrence) for each score. We also determined the weighted net benefit based on the arbitrary assumption that a missed major bleeding event is 10 times worse than to be left unnecessarily at risk of recurrent VTE (TP-[FP/10])/[TP+TN+FN+FP], where TP refers to the true positive, FP to the false positive, TN to the true negative, and FN to false negative rate) (25). A positive net benefit value indicates that the benefit of withholding extended anticoagulation in patients at high risk of major bleeding (and thus preventing potential bleeding events) exceeds the risks to develop recurrent VTE. A negative value indicates that the harm of withholding extended anticoagulation in patients who are at high risk of bleeding (and thus exposing them to the risk of recurrent VTE) exceeds the potential benefit of preventing major bleeding events. The statistical analyses were done using Stata 15 (Stata Corporation, College Station, TX, USA).

RESULTS

Study sample

Of the 1003 patients enrolled in the SWITCO 65+ study, we excluded 12 patients who denied the use of their data or withdrew their consent early after enrolment. After the additional exclusion of 248 patients who did not continue oral anticoagulation beyond 3 months after the index VTE or had less than two INR measurements, our final study sample comprised 743 elderly patients with VTE receiving extended oral anticoagulation. Excluded patients did not differ from analyzed patients in terms of age or sex, but were less likely to have pulmonary embolism as the index VTE (52% vs. 75%; $p<0.001$). The median age of analyzed patients was 75 years (interquartile range [IQR] 70-81 years) (Table 1). Patients who experienced a first major bleeding during extended anticoagulation were more likely to have had major bleeding during the initial 3 months of anticoagulation, a history of coronary heart disease, a low physical activity level, or <30% of INR values within the therapeutic range than patients without major bleeding (Table 1). Among the 10 evaluated scores, only the Seiler, RIETE, and ATRIA scores had significantly higher median score points in patients with a major bleeding than in those without.

Comparison of risk classification and bleeding incidences

During a median extended anticoagulation duration of 10.1 months (IQR 3.5-26.6 months), 45 patients (6.1%) experienced a first major and 127 (17.1%) a clinically relevant bleeding episode. Of the 45 major bleeds, 18 (40%) were gastrointestinal, 7 (16%) were intracranial, and 2 (4.4%) were fatal. Of the 96 clinically relevant non-major bleedings, the most common bleeding localizations were (sub-)cutaneous (40%) and urogenital (18%) bleeds, and epistaxis (18%). The incidence rate of a first major and clinically relevant bleeding was 4.9 (95%

confidence interval [CI] 3.7-6.6) and 15.0 (95% CI 12.6-17.9) events per 100 patient-years, respectively. The cumulative bleeding incidences at 36 months are shown in Figure 1. The proportion of patients classified as high-risk varied between 6% (OBRI) and 94% (ACCP) (Table 2). The incidence rate of a first major bleeding ranged from 0 (ACCP) to 5.0 events per 100 patient-years (OBRI) in lower-risk patients and from 3.4 (OBRI) to 12.2 events per 100 patient-years (Seiler) in high-risk patients (Table 2). The incidence of clinically relevant bleeding varied between 1.7 (ACCP) and 14.5 events per 100 patient-years (OBRI) in lower-risk patients and between 16.0 (ACCP) and 32.6 events per 100 patient-years (Seiler) in high-risk patients.

Comparison of predictive accuracy, discriminative power, and calibration

When dichotomized as lower- vs. high-risk, the positive LHR for a first major bleeding varied between 0.69 (OBRI) and 2.56 (Seiler) (Table 3). The positive LHR for a first clinically relevant bleeding event ranged from 1.07 (ACCP) to 2.36 (Seiler) (Table 3). The negative LHRs for major and clinically relevant bleeding were generally >0.5, with the exception for the ACCP, which showed a negative LHR of 0.17 for major and 0.11 for clinically relevant bleeds.

The discriminative power (area under the ROC curve) of the individual scores to predict a first major bleeding and a first clinically relevant bleeding varied from 0.47 (OBRI) to 0.70 (Seiler) and from 0.52 (OBRI) to 0.67 ($HEMORR_2HAGES$), respectively (Table 4). The calibration of all bleeding risk scores except for the $HEMORR_2HAGES$ ($p=0.01$) was adequate ($p>0.05$).

Analysis of clinical impact

Based on the assumption that patients classified as high-risk were not to receive and patients classified as lower-risk were to receive extended

anticoagulation, the unweighted net benefit (i.e., % of potentially avoided first major bleedings minus % of patients left at risk of VTE recurrence) of the scores ranged from -81.8% (ACCP) to -5.8% (OBRI). The weighted net benefit, assuming an unavoided major bleeding event (false negative rate) to be 10 times worse than an unnecessary exposure to the risk of recurrent VTE (false positive rate), ranged from -2.7% (ACCP) to 0.8% (Seiler) (Table 5).

DISCUSSION

Our prospective head-to-head comparison demonstrated that in elderly patients with VTE most bleeding risk scores did not have an adequate accuracy and power to discriminate between those with a high risk of bleeding during extended anticoagulation and those without. Only half of the 10 scores identified a high-risk group of patients with an annual bleeding rate of ≥6.5% (Seiler, Kuijer, RIETE, $HEMORR_2HAGES$, ATRIA), a cut-off that has been used to define a high major bleeding risk (1). Moreover, only 2 scores demonstrated a positive LHR for major bleeding (Seiler, RIETE) and clinically relevant bleeding (Seiler, $HEMORR_2HAGES$) above 2. A positive LHR above 2 indicates a small, albeit potentially clinically useful change in post-test probability (26). The discriminative power of the 10 scores for major bleeding was poor to fair at best, with the area under the ROC curve varying from 0.47 (OBRI) to 0.70 (Seiler). Interestingly, the predictive performance of most VTE-specific and non-VTE-specific scores was quite similar. Finally, our results suggest that many patients would be left at risk of recurrent VTE if only patients classified as non-high risk were to receive extended anticoagulation. Even if a avoided major bleeding was assumed to be 10 times worse than to be left at risk of VTE recurrence, the weighted net benefit of score use was marginal, ranging from -2.7% (ACCP, worst) to 0.8% (Seiler, best).

Overall, the only score with an acceptable predictive performance for major bleeding during extended anticoagulation was the Seiler score. This is not astonishing, given that the Seiler score was specifically developed to predict major bleeding in elderly patients who receive anticoagulants for >3 months using data from the same cohort (SWITCO65+) on which the present analysis is based. Thus, the predictive performance of the Seiler score requires external validation before its use can be recommended.

The VTE-BLEED, which was developed to predict bleeding events under stable anticoagulation (i.e., after the first month) over 6 months using data from 2 randomized trials (mean patient age 55 years), did not perform particularly well in our cohort of elderly patients, with an area under the ROC curve of 0.57 for major bleeding compared to a c-statistic of 0.72 in the original derivation cohort (6).

Given the heterogeneity of the scores in terms of number/type of predictors as well as score weights, the proportion of patients classified as high-risk varied widely among the bleeding risk scores and ranged from 6% (OBRI) to 94% (ACCP). Thus, in the elderly with VTE, the clinical usefulness of the OBRI and ACCP score may be additionally limited by floor and ceiling effects.

To our knowledge, our study is the first comparison of the predictive performance of clinical bleeding risk scores during extended anticoagulation in elderly patients with VTE. Our results are consistent with prior studies demonstrating that OBRI and the Kuijer, RIETE, and Kearon scores also have a poor predictive performance for the first 3 months of anticoagulant treatment and over the entire anticoagulation period in elderly patients receiving VKAs for VTE (area under the ROC curves ranging from 0.49 to 0.60) (23). A prospective cohort study of 1078 very old patients on VKA treatment for secondary prevention of VTE found a poor predictive performance for the OBRI, HEMORR$_2$HAGES, RIETE, HAS-BLED, ATRIA, and ACCP scores (c-statistic 0.55-0.61) (27). In another prospective study comparing 7 bleeding risk scores in 515 patients receiving VKAs, predictive score performance was also poor and no better than physicians' subjective risk assessment (28). Prior evidence also suggests that bleeding risk models (HEMORR$_2$HAGES, HAS-BLED, ATRIA) have a poor discriminative power in elderly patients with atrial fibrillation (c-statistic <0.60 for major bleeding) (29).

Potential reasons why bleeding risk scores do not perform well in the anticoagulated elderly include the underrepresentation of older patients in the derivation studies, non-inclusion of bleeding risk predictors that may be relevant in the elderly (e.g., physical activity level, polypharmacy, multimorbidity), and a lack of appropriate statistical derivation techniques (7). However, given the clinical complexity of many multimorbid, polymedicalized elderly patients, it is also possible that a static clinical model-based bleeding risk stratification is doomed to failure. If so, the future research focus should lie on the development of elderly-friendly anticoagulation strategies using safer direct anticoagulants and reduced treatment doses and durations (30-32).

Our study has several limitations. First, our analysis included only elderly patients receiving extended anticoagulation for VTE, and thus our results cannot be generalized to younger persons or those with other anticoagulation indications. A study comparing 7 clinical bleeding risk scores in younger patients (mean age 55 years) with VTE who were under stable anticoagulation with warfarin found a higher discriminative power for bleeding events (c-statistic 0.65-0.78) (6), but others did not (33). Second, our study patients were all treated with VKAs. Therefore, our findings may not be applicable to patients treated with direct oral anticoagulants that carry somewhat lower absolute bleeding risks than VKAs (34). To our knowledge, only one bleeding risk score, the VTE-BLEED, has been derived in patients treated with a direct oral anticoagulant (dabigatran) but has not yet been specifically validated in the elderly with VTE. Third, as we included patients who received anticoagulation treatment with VKAs only, patients with cancer who may receive extended treatment with low-molecular-weight heparin rather than with VKAs may be underrepresented in our study. In addition, we included only surviving patients who were still under VKAs at 3 months following the index VTE, which may further explain the lower

proportion of patients with cancer and may have resulted in a lower case-fatality rate of subsequent major bleeding events (healthy survivor bias). Fourth, because peptic ulcer disease was not recorded in our database, we assumed this variable to be normal when calculating the Kearon score. Thus, it is possible that our analysis underestimated the bleeding risk in the high-risk category of this score. We also assumed missing score values to be normal, a strategy widely used in the clinical application of prognostic models (35, 36). Overall, we had few missing values in our database (see Table 1). Fifth, the number of events per risk group was very low for several scores (e.g., only 2 major bleeding events in the OBRI high risk group), resulting in wide confidence intervals. Furthermore, the median extended anticoagulation duration of 10.1 months was relatively short, whereas anticoagulation is often continued for years in clinical practice. Thus, we cannot exclude the possibility that bleeding events at a later time point were missed, which may have decreased the prognostic performance of scores that were derived using longer follow-up periods (Kearon, OBRI, HEMORR$_2$HAGES, ATRIA). Finally, while we examined score performance during extended anticoagulation (i.e., >3 months after the index VTE), we based our score calculations on patient baseline characteristics. Therefore, potential changes in bleeding risk factors (trauma, surgery) during the initial 3 months or later during follow-up were not taken into account, as they should be in clinical practice.

In conclusion, our findings indicate that, with the potential exception of the Seiler score, existing bleeding risk scores do not have sufficient predictive accuracy and discriminative power to identify elderly patients with VTE who are at high risk of bleeding during extended treatment with VKAs. Thus, these scores do not appear to be useful for identifying high-risk patients with VTE who are unsuitable candidates for extended anticoagulation.

CONFLICTS OF INTEREST

The authors state that they have no conflicts of interest.

AUTHORSHIP DETAILS

A.N. Frei and D. Aujesky were responsible for study concept and design. O. Stalder and A. Limacher carried out the statistical analyses. A.N. Frei and D. Aujesky wrote the manuscript. O. Stalder, A. Limacher, M. Méan, C. Baumgartner, and N. Rodondi revised the manuscript. M. Méan and D. Aujesky collected data and obtained funding from the Swiss National Science Foundation.

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FIGURE LEGENDS

Figure

Panel A) Cumulative incidence of a first major bleeding during extended anticoagulation

Panel B) Cumulative incidence of a first clinically relevant bleeding during extended anticoagulation

Table 1 Patient baseline characteristics

Characteristics*	All (N = 743)	Major bleeding (N = 45)	No major bleeding (N = 698)
	Percentage or median (interquartile range)		
Age, years	75 (70-81)	77 (69-81)	75 (70-81)
Male sex	53	51	53
Index VTE event			
DVT only	25	22	25
PE ± DVT	75	78	75
Unprovoked†	69	62	70
Provoked	21	22	21
Cancer-related	10	16	9
Medical history			
History of major bleeding	9	7	9
Recent major surgery‡	13	18	13
Major bleeding during first 3 months of anticoagulation	4	11	3
Previous gastrointestinal bleeding§	4	0	5
History of stroke¶	9	4	9
Coronary heart disease	17	31	16
Recent myocardial infarction**	1	2	0
Peripheral artery disease	6	13	6
Arterial hypertension	65	67	65
Diabetes mellitus	16	9	16
Chronic renal disease††	18	27	18
Chronic liver disease‡‡	1	22	1
Chronic lung disease§§	13	13	13
Alcohol abuse¶¶	19	9	20
Active cancer***	10	16	9
Metastatic cancer†††	2	4	2
Low physical activity‡‡‡	34	58	32
High risk of falls§§§	44	49	43
Antiplatelet¶¶¶ or NSAID therapy	39	51	38
Clinical and laboratory findings at baseline			
Systolic blood pressure, mmHg			
≥140	47	40	47
>160	14	16	13
Anemia			
Hb <130g/l in men, Hb<120g/l in women	33	51	32
Hb <120g/l in men, Hb<110g/l in women	21	29	20
Hematocrit <30%****	9	4	9
Thrombocytopenia (<150G/l)	14	11	14
Creatinine clearance, ml/min††††			
30-60	30	36	29
<30	5	9	5
Serum creatinine, µmol/l			
>106	23	33	22
>133	10	18	9
≥200	3	7	3
≥221	3	4	3
Genetic factors: CYP2C9 variants	33	38	32

Cont.

Cont.

Characteristics*	All (N = 743)	Major bleeding (N = 45)	No major bleeding (N = 698)
	Percentage or median (interquartile range)		
Score, number of points			
VTE-BLEED	3.0 (1.5-3.5)	3.0 (1.5-4.5)	3.0 (1.5-3.0)
Seiler	2.0 (1.0-3.0)	3.0 (2.0-4.0)	2.0 (1.0-3.0)
Kuijer	2.9 (1.6-2.9)	2.9 (1.6-2.9)	2.9 (1.6-2.9)
Kearon	2.0 (1.0-3.0)	2.0 (1.5-3.0)	2.0 (1.0-3.0)
RIETE	2.0 (1.0-3.5)	2.5 (2.0-4.0)	2.0 (1.0-3.5)
ACCP	4.0 (3.0-6.0)	5.0 (4.0-6.5)	4.0 (3.0-6.0)
OBRI	1.0 (1.0-2.0)	1.0 (1.0-2.0)	1.0 (1.0-2.0)
HAS BLED	3.0 (2.0-3.0)	3.0 (2.0-4.0)	3.0 (2.0-3.0)
HEMORR2AGES	3.0 (2.0-4.0)	3.0 (1.0-4.0)	3.0 (2.0-4.0)
ATRIA	3.0 (1.0-4.0)	4.0 (2.0-5.5)	3.0 (1.0-4.0)
Quality of AC during first 3 months on VKA			
<30% of measured INR values in therapeutic range‡‡‡‡	19	33	19
Percentage of time in INR range§§§§			
INR <2	21 (7-40)	24 (16-55)	21 (6-40)
INR 2-3	58 (38-78)	58 (31-72)	58 (39-78)
INR >3	9 (0-24)	7 (0-23)	9 (0-24)

Abbreviations: VTE = venous thromboembolism; DVT = deep vein thrombosis; PE = pulmonary embolism; NSAID = non-steroidal anti-inflammatory drugs; Hb = haemoglobin; AC = anticoagulation; VKA = vitamin K antagonists; INR = international normalized ratio

*Data were missing for history of major bleeding (0.1%), alcohol abuse (0.4%), physical activity (0.3%), risk of fall (0.1%), blood pressure (1.5%), hemoglobin (6.5%), thrombocyte count (6.6%), serum creatinine level (7.9%), and genetic factors (10%)

†VTE that is not associated with an environmental risk factor

‡Surgery requiring general or spinal anaesthesia during the last 3 months

§Any previous gastrointestinal bleeding leading to hospital admission or transfusions

¶History of ischemic or hemorrhagic stroke, or a transient ischemic attack

**Myocardial infarction with or without ST-elevation (STEMI or NSTEMI) during the last 3 months

††Chronic renal failure (requiring haemodialysis or not), such as diabetic or hypertensive nephropathy, chronic glomerulonephritis, chronic interstitial nephritis, myeloma-related nephropathy, or cystic kidney disease

‡‡Liver cirrhosis, chronic hepatitis, chronic liver failure, or hemochromatosis

§§Chronic obstructive pulmonary disease (COPD), active asthma, lung fibrosis, cystic fibrosis, or bronchiectasis

¶¶Consumption of >8 units of alcoholic beverages per week

***Solid or hematologic cancer treated with chemotherapy, radiotherapy, surgery, or palliative care during the last 3 months; local skin tumors such as basal cell carcinomas and spinal cell carcinomas were not considered as cancer

†††Active cancer with known metastases

‡‡‡The patient is either mostly sitting/lying and does not move a lot, or often walks but avoids to climb stairs or to carry light weight < 5 kg (self-reported)

§§§≥1 of following screening questions answered with yes: (i) Did you fall during the last year? (ii) Did you notice any problems with gait, balance, or mobility?

¶¶¶Co-medication with aspirin, clopidogrel, prasugrel, or ticagrelor

****Calculated by multiplying the hemoglobin level in g/l by 0.3

††††Calculated based on the Cockroft-Gault formula

‡‡‡‡INR 2.0-3.0

§§§§Based on the Rosendaal linear interpolation method (21)

Table 2 Risk classification and incidence rates of a first major and clinically relevant bleeding episode during extended anticoagulation*

	Risk classification		Major bleeding (n=45)			Clinically relevant bleeding (n=127)		
Prediction score category †	n	%	n	Median duration of AC, months (IQR)	Incidence rates per 100py (95% CI)	n	Median duration of AC, months (IQR)	Incidence rates per 100py (95% CI)
VTE-BLEED								
Lower risk	244	33	12	10.2 (3.4-26.7)	3.9 (2.2-6.9)	33	9.5 (3.2-23.4)	11.6 (8.2-16.3)
High risk	499	67	33	10.0 (3.5-26.5)	5.4 (3.8-7.6)	94	8.7 (3.3-21.8)	16.7 (13.7-20.5)
Seiler								
Lower risk	630	85	29	10.0 (3.5-26.6)	3.7 (2.6-5.3)	90	9.1 (3.4-24.2)	12.3 (10.0-15.1)
High risk	113	15	16	10.4 (3.3-22.6)	12.2 (7.5-19.9)	37	7.6 (2.8-20.8)	32.6 (23.6-45.0)
Kuijer								
Lower risk	672	90	38	10.2 (3.6-26.7)	4.5 (3.3-6.2)	109	9.3 (3.4-23.7)	13.9 (11.5-16.8)
High risk	71	10	7	7.0 (2.8-20.9)	9.5 (4.5-19.8)	18	5.9 (2.4-20.7)	28.0 (17.6-44.4)
Kearon								
Lower risk	529	71	31	9.7 (3.5-26.5)	4.8 (3.4-6.8)	81	8.8 (3.3-22.4)	13.5 (10.9-16.8)
High risk	214	29	14	12.7 (3.5-26.7)	5.1 (3.0-8.6)	46	9.3 (3.1-22.9)	18.5 (13.9-24.7)
RIETE								
Lower risk	675	91	37	10.2 (3.5-26.6)	4.4 (3.2-6.1)	109	9.2 (3.3-23.7)	14.0 (11.6-16.9)
High risk	68	9	8	8.8 (3.5-21.0)	10.5 (5.3-21.0)	18	5.9 (3.3-20.8)	26.7 (16.8-42.4)
ACCP								
Lower risk	45	6	0	8.9 (3.7-27.6)	0.0 (-)	1	8.9 (3.7-27.6)	1.7 (0.2-12.2)
High risk	698	94	45	10.2 (3.5-26.5)	5.2 (3.9-7.0)	126	9.0 (3.3-21.8)	16.0 (13.4-19.0)
OBRI								
Lower risk	696	94	43	9.9 (3.5-26.6)	5.0 (3.7-6.7)	115	8.9 (3.3-22.8)	14.5 (12.1-17.4)
High risk	47	6	2	12.8 (4.5-26.8)	3.4 (0.8-13.4)	12	10.4 (3.8-21.2)	22.4 (12.7-39.4)
HAS-BLED								
Lower risk	350	47	19	9.9 (3.6-26.5)	4.4 (2.8-7.0)	47	9.0 (3.3-23.9)	11.6 (8.7-15.5)
High risk	393	53	26	10.5 (3.5-26.7)	5.3 (3.6-7.8)	80	9.0 (3.3-21.5)	18.1 (14.5-22.5)
$HEMORR_2HAGES$								
Lower risk	539	73	26	9.8 (3.5-26.4)	4.0 (2.7-5.8)	61	9.3 (3.4-23.9)	9.7 (7.6-12.5)
High risk	204	27	19	12.4 (3.7-26.8)	7.2 (4.6-11.3)	66	7.7 (3.0-21.0)	29.9 (23.5-38.0)
ATRIA								
Lower risk	571	77	27	10.3 (3.6-26.7)	3.8 (2.6-5.5)	88	9.3 (3.4-24.7)	13.2 (10.7-16.2)
High risk	172	23	18	9.9 (3.3-22.5)	9.0 (5.7-14.3)	39	7.1 (3.0-20.9)	21.9 (16.0-30.0)

Abbreviations: AC = anticoagulation; IQR = interquartile range; py = patient-years; CI = confidence interval

*Extended anticoagulation is the period between day 90 after the index VTE and the end of the initially prescribed anticoagulant treatment

†3-level scores were dichotomized as lower (low- or moderate risk) vs. high risk

Table 3 Accuracy for predicting a first major and clinically relevant bleeding during extended anticoagulation*

	Positive LHR (95% CI)	Negative LHR (95% CI)
First major bleeding		
VTE-BLEED	1.10 (0.91-1.32)	0.80 (0.49-1.32)
Seiler	2.56 (1.66-3.95)	0.75 (0.60-0.93)
Kuijer	1.70 (0.83-3.48)	0.93 (0.82-1.06)
Kearon	1.09 (0.69-1.70)	0.97 (0.79-1.18)
RIETE	2.07 (1.05-4.06)	0.90 (0.78-1.03)
ACCP	1.07 (1.05-1.09)	0.17 (0.01-2.67) †
OBRI	0.69 (0.17-2.75)	1.02 (0.96-1.09)
HAS-BLED	1.10 (0.85-1.42)	0.89 (0.63-1.26)
$HEMORR_2HAGES$	1.59 (1.11-2.29)	0.79 (0.61-1.01)
ATRIA	1.81 (1.23-2.66)	0.77 (0.60-0.98)
First clinically relevant bleeding		
VTE-BLEED	1.13 (1.00-1.27)	0.76 (0.55-1.04)
Seiler	2.36 (1.68-3.33)	0.81 (0.72-0.91)
Kuijer	1.65 (1.00-2.71)	0.94 (0.87-1.01)
Kearon	1.33 (1.02-1.73)	0.88 (0.76-1.01)
RIETE	1.75 (1.06-2.89)	0.93 (0.87-1.01)
ACCP	1.07 (1.04-1.10)	0.11 (0.02-0.79)
OBRI	1.66 (0.89-3.11)	0.96 (0.90-1.02)
HAS-BLED	1.24 (1.06-1.45)	0.75 (0.59-0.96)
$HEMORR_2HAGES$	2.32 (1.86-2.90)	0.62 (0.51-0.75)
ATRIA	1.42 (1.05-1.92)	0.88 (0.78-1.00)

Abbreviations: LHR = likelihood ratio; CI = confidence interval

*Extended anticoagulation is the period between day 90 after the index VTE and the end of the initially prescribed anticoagulant treatment

† Computed using the continuity correction

Table 4 Discriminative power to predict a first major and clinically relevant bleeding during extended anticoagulation* and score calibration

	Area under the ROC curve (95% CI)	p-value†	Score calibration‡
First major bleeding			
VTE-BLEED	0.57 (0.53-0.61)	0.11	0.11
Seiler	0.70 (0.66-0.73)	<0.001	0.20
Kuijer	0.55 (0.51-0.59)	0.23	0.71
Kearon	0.53 (0.50-0.57)	0.41	0.93
RIETE	0.63 (0.59-0.66)	<0.001	0.95
ACCP	0.59 (0.55-0.62)	0.03	0.14
OBRI	0.47 (0.43-0.51)	0.37	0.92
HAS-BLED	0.54 (0.50-0.58)	0.41	0.65
$HEMORR_2HAGES$	0.57 (0.53-0.60)	0.16	< 0.001
ATRIA	0.61 (0.57-0.64)	0.02	0.21
First clinically relevant bleeding			
VTE-BLEED	0.58 (0.55-0.62)	<0.001	0.64
Seiler	0.66 (0.62-0.69)	<0.001	0.72
Kuijer	0.54 (0.50-0.57)	0.19	0.52
Kearon	0.58 (0.54-0.61)	<0.001	0.63
RIETE	0.62 (0.58-0.65)	<0.001	0.49
ACCP	0.65 (0.61-0.68)	<0.001	0.26
OBRI	0.52 (0.48-0.56)	0.41	0.22
HAS-BLED	0.60 (0.56-0.63)	<0.001	0.42
$HEMORR_2HAGES$	0.67 (0.63-0.70)	<0.001	0.01
ATRIA	0.60 (0.56-0.63)	<0.001	0.40

Abbreviations: ROC = receiver operator characteristic, CI = confidence interval

*Extended anticoagulation is the period between day 90 after the index VTE and the end of the initially prescribed anticoagulant treatment

†A value <0.05 indicates that the discriminative power to predict a first bleeding event is statistically significantly different from chance (i.e. an area under the ROC curve of 0.5)

‡p-values from Pearson chi-square goodness-of-fit test

Table 5 Net benefit of score use

Risk score	TP	TN	FN	FP	Percentage of potentially avoided major bleedings*	Percentage of patients left unnecessarily at risk of recurrent VTE†	Unweighted net benefit‡	Weighted net benefit§
	n				%			
VTE-BLEED	33	232	12	466	4.4	62.7	-58.3	-1.8
Seiler	16	601	29	97	2.2	13.1	-10.9	0.8
Kuijer	7	634	38	64	0.9	8.6	-7.7	0.1
Kearon	14	498	31	200	1.9	26.9	-25.0	-0.8
RIETE	8	638	37	60	1.1	8.1	-7.0	0.3
ACCP	45	45	0	653	6.1	87.9	-81.8	-2.7
OBRI	2	653	43	45	0.3	6.1	-5.8	-0.3
HAS-BLED	26	331	19	367	3.5	49.4	-45.9	-1.4
HEMORR$_2$HAGES	19	513	26	185	2.6	24.9	-22.3	0.1
ATRIA	18	544	27	154	2.4	20.7	-18.3	0.3

Abbreviations: TP = true positive; TN = true negative; FN = false negative; FP = false positive; VTE = venous thromboembolism

*Potentially avoided major bleedings if high-risk patients were not to receive and non-high-risk patients were to receive extended anticoagulation (TP/[TP+FP+TN+FN])

†Based on the assumption that extended anticoagulation would be withheld in all high-risk patients, thus unnecessarily exposing those who do not develop bleeding complications to the risk of VTE recurrence (FP/[TP+FP+TN+FN])

‡Percentage of potentially avoided first major bleedings minus the percentage of patients left at risk of recurrent VTE

§Net benefit assuming that a missed major bleeding is 10 times worse than to be unnecessarily left at risk of recurrent VTE (TP-[FP/10])/[TP+TN+FN+FP])

APPENDIX

Appendix Table Bleeding risk scores

Score	a. Design of derivation study b. Sample size c. Patient age d. Length of follow-up e. Indication for AC	Variables	Score points	Outcome definition of bleeding	Risk categories	
VTE-BLEED **(6)**	a. Retrospective	Active cancer	2	Major bleeding according to the International Society on Thrombosis and Haemostasis (ISTH) (22) (22)*	Low risk	<2 points
	b. 2553	Male patient with uncontrolled hypertension	1		High risk	≥2 points
	c. 55 years (average)	Anemia	1.5			
	d. 6 months	History of bleeding	1.5			
	e. VTE	Renal dysfunction	1.5			
		Age ≥60 years	1.5			
Seiler **(7)**	a. Retrospective	Previous major bleeding	1	Major bleeding, according to the ISTH (22)	Low risk	0-1 points
	b. 743	Active cancer	1		Moderate risk	2-3 points
	c. 75 years (median)	Low physical activity	2		High risk	≥4 points
	d. 16 months (median)	Anemia	1			
	e. VTE	Thrombocytopenia	1			
		Antiplatelet drugs or NSAIDs	1			
		Poor INR control	1			
Kuijer **(8)**	a. Retrospective	Age ≥60 years	1.6	Major bleeding, defined as decline in hemoglobin concentration of ≥20 g/l, need for transfusion of ≥2 units of red blood cells, located retroperitoneal or intracranial, or warranting a permanent discontinuation of treatment	Low risk	0 points
	b. 241	Female sex	1.3		Moderate risk	1-2 points
	c. 63 years (average)	Malignancy	2.2		High risk	≥3 points
	d. 3 months					
	e. VTE					
Kearon **(9)**	a. Prospective	Age ≥65 years	1	Major bleeding according to the ISTH (22)	Low risk	0-1 points
	b. 738	Prior stroke	1		Moderate risk	2 points
	c. 57 years (average)	Prior peptic ulcer disease	1		High risk	≥3 points
	d. 2.4 years (average)	Prior gastrointestinal bleeding	1			
	e. Unprovoked VTE	Creatinine >1.5 mg/dl (=133µmol/l)	1			
		Anemia or thrombocytopenia	1			
		Liver disease	1			
		Diabetes mellitus	1			
		Antiplatelet therapy	1			
RIETE **(10)**	a. Retrospective	Recent major bleeding	2	Major bleeding, defined as fatal bleeding, or bleeding requiring transfusion of ≥2 units of blood or located retroperitoneal, spinal or intracranial	Low risk	0 points
	b. 13 057	Creatinine >1.2mg/dl (=106µmol/l)	1.5		Moderate risk	1-4 points
	c. 66 years (average)	Anemia	1.5		High risk	>4 points
	d. 3 months	Malignancy	1			
	e. VTE	Clinically overt pulmonary embolism	1			

Cont.

Cont.

Score	a. Design of derivation study b. Sample size c. Patient age d. Length of follow-up e. Indication for AC	Variables	Score points	Outcome definition of bleeding	Risk categories	
ACCP **(1)**	Combined evidence from many previous studies	Age >65 years	1	No uniform definition of bleeding (combination of many previous studies)	Low risk	0 points
		Age >75 years	1		Moderate risk	1 point
		Previous bleeding	1		High risk	≥2 points
		Cancer	1			
		Metastatic cancer	1			
		Renal failure	1			
		Liver failure	1			
		Thrombocytopenia	1			
		Previous stroke	1			
		Diabetes mellitus	1			
		Anemia	1			
		Antiplatelet therapy	1			
		Poor anticoagulant control	1			
		Comorbidity	1			
		Recent surgery	1			
		Frequent falls	1			
		Alcohol abuse	1			
OBRI **(15)**	a. Retrospective	Age ≥65 years	1	Major bleeding, defined as overt bleeding that led to the loss of at least 2 units in 7 days or less, or was otherwise life-threatening (e.g. intracranial bleeding)	Low risk	0 points
	b. 556	History of stroke	1		Moderate risk	1-2 points
	c. 61 years (average)	History of gastrointestinal bleeding	1		High risk	3-4 points
	d. 48 months	Specific comorbidities - Recent myocardial infarction - Severe anemia - Renal insufficiency - Diabetes mellitus	1			
	e. Mixed (VTE in 15%)					
HAS-BLED **(12)**	a. Prospective	Hypertension	1	Major bleeding, defined as any bleeding requiring hospitalization and/or causing a decrease in hemoglobin level of ≥20 g/l and/or requiring blood transfusion and that was not a hemorrhagic stroke	Low risk	0 points
	b. 2115	Abnormal renal or liver function	1 or 2		Moderate risk	1-2 points
	c. 66.8 years (average)	Stroke	1		High risk	≥3 points
	d. 1 year	Bleeding history or predisposition	1			
	e. AF	Labile INR on vitamin K antagonists	1			
		Elderly	1			
		Drugs or alcohol	1 or 2			

Cont.

Cont.

Score	a. Design of derivation study b. Sample size c. Patient age d. Length of follow-up e. Indication for AC	Variables	Score points	Outcome definition of bleeding	Risk categories	
HEMORR$_2$HAGES **(13)**	a. Retrospective	Hepatic or renal disease	1	Hospitalization for hemorrhage based on	Low risk	0-1 points
	b. 1 604	Ethanol abuse	1	ICD-9-CM codes	Moderate risk	2-3 points
	c. 79 years (average)	Malignancy	1		High risk	≥4 points
	d. 36 months	Older age	1			
	e. AF	Reduced platelet count or function	1			
		Rebleeding risk	1			
		Hypertension (uncontrolled)	1			
		Anemia	1			
		Genetic factors	1			
		Excessive fall risk	1			
		Stroke	1			
ATRIA **(14)**	a. Retrospective	Anemia	3	Major bleeding according to ISTH (22)	Low risk	0-3 points
	b. 6 123	Severe renal disease	3		Moderate risk	4 points
	c. Majority >65years	Age ≥75 years	2		High risk	5-10 points
	d. 3.5 years	Any prior hemorrhage diagnosis	1			
	e. AF	Diagnosed hypertension	1			

Abbreviations: AC = anticoagulation; VTE = venous thromboembolism; NSAID = non-steroidal anti-inflammatory drugs; INR = international normalized ratio; AF = atrial fibrillation

*major bleeding defined as fatal bleeding, symptomatic bleeding in a critical area (intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, intramuscular with compartment syndrome), or bleeding resulting in a drop of the hemoglobin level of ≥20 g/l or leading to transfusion of ≥2 units of red blood cells