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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.

65 **BACKGROUND**

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

75 The estimation of the bleeding risk under anticoagulant treatment is complex,
76 as the propensity to bleed is influenced by multiple intercurrent and permanent
77 patient and treatment factors (5). To facilitate physician decision-making, several
78 clinical scores have been derived and validated to predict the short- or longer-term
79 risk of anticoagulation-related bleeding in patients with acute VTE or other diseases
80 (1, 6-14). However, with the exception of the VTE-BLEED and Seiler scores (6, 7),
81 which were derived to predict bleeding occurring after the period of the first 1-3
82 months of anticoagulant therapy, most scores either focused on the initial 3 months
83 (8, 10) or the entire anticoagulation period (12-15).

84 Elderly patients do not only represent the majority of cases of VTE (16), they
85 also have a 2-fold increased risk of major and clinically relevant non-major bleeds
86 compared to younger patients (3, 4). Therefore, we aimed to compare the predictive
87 performance of commonly cited bleeding risk scores for VTE and other conditions
88 during extended anticoagulant therapy with VKAs in elderly patients with VTE. We
89 focused on the question whether the scores accurately identify elderly patients at
90 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

117 conditions (cancer, cardiorespiratory diseases, diabetes mellitus, chronic liver and
118 renal disease), physical examination (blood pressure) and laboratory findings
119 (hemoglobin, platelet count, creatinine), concomitant antiplatelet therapy, and VTE-
120 related treatments. In patients who gave their consent, an additional blood sample
121 was stored for analysis of genetic risk factors that may influence the risk of bleeding
122 (i.e., presence of CYP2C9 variants).
123
124 **Risk assessment scores**
125 Using baseline on demographics and clinical data obtained by chart review,
126 we determined the presence of the prognostic variables comprising bleeding risk
127 scores validated for VTE (VTE-BLEED, Seiler, Kuijer, Kearon, RIETE and ACCP
128 score) or other diseases, predominantly atrial fibrillation (Outpatient Bleeding Risk
129 Index [OBRI], HAS-BLED, HEMORR$_2$HAGES, and ATRIA score) (6-14, 18). Based
130 on the prognostic variables, we calculated the 10 prognostic scores and classified
131 each patient in the low- and high-risk (VTE-BLEED) or in the low-, intermediate-, or
132 high-risk category (all other scores; Appendix Table). To ensure comparability, 3-
133 level scores were further dichotomized as lower (low- or moderate risk) vs. high risk.
134 As done in the original derivation studies, the scores were generally calculated using
135 patient data at the time of the index VTE. Exceptions were the variables with regard
136 to poor anticoagulation/INR control (Seiler, ACCP, and HAS-BLED) and the Seiler
137 score variable “previous major bleeding”, which were assessed at the end of the
138 initial 3 months of anticoagulant therapy.
139 Missing values and score variables not documented in our database (peptic
140 ulcer disease) were assumed to be normal. The hematocrit was calculated by
141 multiplying the hemoglobin level in g/l by 0.3 (19). Whenever possible, we used the
142 exact variable definition as per the original derivation study. When the definition was

143 not specified or differed from the data available in our database, we used
144 standardized proxy definitions (e.g., platelet count <150 G/l for thrombocytopenia).
145 For instance, we defined “active cancer” or “malignancy” as the presence of a solid or
146 hematologic cancer under chemotherapy, radiotherapy, surgery, and/or palliative
147 care during the 3 months prior to the index VTE. A “history of bleeding”, “previous
148 (major) bleeding”, “recent major bleeding”, “any prior hemorrhage diagnosis”, or “re-
149 bleeding risk” was defined as a bleeding that led to a hospital stay or transfusion. We
150 defined a “history of stroke”, “prior or previous stroke”, or “stroke” as a history of
151 ischemic/hemorrhagic stroke or a transient ischemic attack. An “excessive fall risk” or
152 “frequent falls” were defined as at least 1 fall during the past year or problems with
153 gait, balance, or mobility (20). We defined alcohol abuse as the consumption of >8
154 units of alcoholic drinks per week (12). Finally, poor anticoagulation/INR control was
155 defined as a time in the therapeutic range (INR 2.0-3.0) of less than 60% based on
156 the Rosendaal method (ACCP, HAS-BLED) or as fewer than 30% of measured INR
157 values in the therapeutic range during the first 3 months of anticoagulation (Seiler) (7,
158 21).
159
160 **Study outcomes**
161 Our primary study outcome was the time to a first major bleeding during
162 extended anticoagulation (i.e., after 3 months) up to 36 months of follow-up. We
163 defined major bleeding as fatal bleeding, symptomatic bleeding in a critical area
164 (intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial,
165 intramuscular with compartment syndrome), or bleeding resulting in a drop of the
166 hemoglobin level of ≥20 g/l or leading to transfusion of ≥2 units of red blood cells
167 (22). The secondary outcome was the time to a first clinically relevant bleeding,
168 defined as the combined outcome of major or clinically relevant non-major bleeding,

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

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

182

183 **Statistical analysis**

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

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

198 We estimated the potential clinical impact of the risk scores by computing the
199 percentage of potentially avoided first major bleedings vs. the percentage of patients
200 left unnecessarily at risk of recurrent VTE if lower-risk patients were to receive and
201 high-risk patients were not to receive extended anticoagulant treatment. We
202 calculated the unweighted benefit (% of avoided first major bleeds minus % of
203 patients left at risk of VTE recurrence) for each score. We also determined the
204 weighted net benefit based on the arbitrary assumption that a missed major bleeding
205 event is 10 times worse than to be left unnecessarily at risk of recurrent VTE (TP-
206 [FP/10])/[TP+TN+FN+FP], where TP refers to the true positive, FP to the false
207 positive, TN to the true negative, and FN to false negative rate) (25). A positive net
208 benefit value indicates that the benefit of withholding extended anticoagulation in
209 patients at high risk of major bleeding (and thus preventing potential bleeding events)
210 exceeds the risks to develop recurrent VTE. A negative value indicates that the harm
211 of withholding extended anticoagulation in patients who are at high risk of bleeding
212 (and thus exposing them to the risk of recurrent VTE) exceeds the potential benefit of
213 preventing major bleeding events. The statistical analyses were done using Stata 15
214 (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%

241 confidence interval [CI] 3.7-6.6) and 15.0 (95% CI 12.6-17.9) events per 100 patient-
242 years, respectively. The cumulative bleeding incidences at 36 months are shown in
243 Figure 1. The proportion of patients classified as high-risk varied between 6% (OBRI)
244 and 94% (ACCP) (Table 2). The incidence rate of a first major bleeding ranged from
245 0 (ACCP) to 5.0 events per 100 patient-years (OBRI) in lower-risk patients and from
246 3.4 (OBRI) to 12.2 events per 100 patient-years (Seiler) in high-risk patients (Table
247 2). The incidence of clinically relevant bleeding varied between 1.7 (ACCP) and 14.5
248 events per 100 patient-years (OBRI) in lower-risk patients and between 16.0 (ACCP)
249 and 32.6 events per 100 patient-years (Seiler) in high-risk patients.
250
251 **Comparison of predictive accuracy, discriminative power, and calibration**
252 When dichotomized as lower- vs. high-risk, the positive LHR for a first major
253 bleeding varied between 0.69 (OBRI) and 2.56 (Seiler) (Table 3). The positive LHR
254 for a first clinically relevant bleeding event ranged from 1.07 (ACCP) to 2.36 (Seiler)
255 (Table 3). The negative LHRs for major and clinically relevant bleeding were
256 generally >0.5, with the exception for the ACCP, which showed a negative LHR of
257 0.17 for major and 0.11 for clinically relevant bleeds.
258 The discriminative power (area under the ROC curve) of the individual scores
259 to predict a first major bleeding and a first clinically relevant bleeding varied from 0.47
260 (OBRI) to 0.70 (Seiler) and from 0.52 (OBRI) to 0.67 (HEMORR$_2$HAGES),
261 respectively (Table 4). The calibration of all bleeding risk scores except for the
262 HEMORR$_2$HAGES (p=0.01) was adequate (p>0.05).
263
264 **Analysis of clinical impact**
265 Based on the assumption that patients classified as high-risk were not to
266 receive and patients classified as lower-risk were to receive extended

267 anticoagulation, the unweighted net benefit (i.e., % of potentially avoided first major
268 bleedings minus % of patients left at risk of VTE recurrence) of the scores ranged
269 from -81.8% (ACCP) to -5.8% (OBRI). The weighted net benefit, assuming an
270 unavoided major bleeding event (false negative rate) to be 10 times worse than an
271 unnecessary exposure to the risk of recurrent VTE (false positive rate), ranged from
272 -2.7% (ACCP) to 0.8% (Seiler) (Table 5).

273 **DISCUSSION**

274 Our prospective head-to-head comparison demonstrated that in elderly
275 patients with VTE most bleeding risk scores did not have an adequate accuracy and
276 power to discriminate between those with a high risk of bleeding during extended
277 anticoagulation and those without. Only half of the 10 scores identified a high-risk
278 group of patients with an annual bleeding rate of ≥6.5% (Seiler, Kuijer, RIETE,
279 HEMORR$_2$HAGES, ATRIA), a cut-off that has been used to define a high major
280 bleeding risk (1). Moreover, only 2 scores demonstrated a positive LHR for major
281 bleeding (Seiler, RIETE) and clinically relevant bleeding (Seiler, HEMORR$_2$HAGES)
282 above 2. A positive LHR above 2 indicates a small, albeit potentially clinically useful
283 change in post-test probability (26). The discriminative power of the 10 scores for
284 major bleeding was poor to fair at best, with the area under the ROC curve varying
285 from 0.47 (OBRI) to 0.70 (Seiler). Interestingly, the predictive performance of most
286 VTE-specific and non-VTE-specific scores was quite similar. Finally, our results
287 suggest that many patients would be left at risk of recurrent VTE if only patients
288 classified as non-high risk were to receive extended anticoagulation. Even if a
289 avoided major bleeding was assumed to be 10 times worse than to be left at risk of
290 VTE recurrence, the weighted net benefit of score use was marginal, ranging from
291 -2.7% (ACCP, worst) to 0.8% (Seiler, best).

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

299 The VTE-BLEED, which was developed to predict bleeding events under
300 stable anticoagulation (i.e., after the first month) over 6 months using data from 2
301 randomized trials (mean patient age 55 years), did not perform particularly well in our
302 cohort of elderly patients, with an area under the ROC curve of 0.57 for major
303 bleeding compared to a c-statistic of 0.72 in the original derivation cohort (6).
304 Given the heterogeneity of the scores in terms of number/type of predictors as
305 well as score weights, the proportion of patients classified as high-risk varied widely
306 among the bleeding risk scores and ranged from 6% (OBRI) to 94% (ACCP). Thus,
307 in the elderly with VTE, the clinical usefulness of the OBRI and ACCP score may be
308 additionally limited by floor and ceiling effects.
309 To our knowledge, our study is the first comparison of the predictive
310 performance of clinical bleeding risk scores during extended anticoagulation in
311 elderly patients with VTE. Our results are consistent with prior studies demonstrating
312 that OBRI and the Kuijer, RIETE, and Kearon scores also have a poor predictive
313 performance for the first 3 months of anticoagulant treatment and over the entire
314 anticoagulation period in elderly patients receiving VKAs for VTE (area under the
315 ROC curves ranging from 0.49 to 0.60) (23). A prospective cohort study of 1078 very
316 old patients on VKA treatment for secondary prevention of VTE found a poor
317 predictive performance for the OBRI, HEMORR$_2$HAGES, RIETE, HAS-BLED, ATRIA,
318 and ACCP scores (c-statistic 0.55-0.61) (27). In another prospective study comparing
319 7 bleeding risk scores in 515 patients receiving VKAs, predictive score performance
320 was also poor and no better than physicians' subjective risk assessment (28). Prior
321 evidence also suggests that bleeding risk models (HEMORR$_2$HAGES, HAS-BLED,
322 ATRIA) have a poor discriminative power in elderly patients with atrial fibrillation (c-
323 statistic <0.60 for major bleeding) (29).

324 Potential reasons why bleeding risk scores do not perform well in the
325 anticoagulated elderly include the underrepresentation of older patients in the
326 derivation studies, non-inclusion of bleeding risk predictors that may be relevant in
327 the elderly (e.g., physical activity level, polypharmacy, multimorbidity), and a lack of
328 appropriate statistical derivation techniques (7). However, given the clinical
329 complexity of many multimorbid, polymedicalized elderly patients, it is also possible
330 that a static clinical model-based bleeding risk stratification is doomed to failure. If so,
331 the future research focus should lie on the development of elderly-friendly
332 anticoagulation strategies using safer direct anticoagulants and reduced treatment
333 doses and durations (30-32).
334 Our study has several limitations. First, our analysis included only elderly
335 patients receiving extended anticoagulation for VTE, and thus our results cannot be
336 generalized to younger persons or those with other anticoagulation indications. A
337 study comparing 7 clinical bleeding risk scores in younger patients (mean age 55
338 years) with VTE who were under stable anticoagulation with warfarin found a higher
339 discriminative power for bleeding events (c-statistic 0.65-0.78) (6), but others did not
340 (33). Second, our study patients were all treated with VKAs. Therefore, our findings
341 may not be applicable to patients treated with direct oral anticoagulants that carry
342 somewhat lower absolute bleeding risks than VKAs (34). To our knowledge, only one
343 bleeding risk score, the VTE-BLEED, has been derived in patients treated with a
344 direct oral anticoagulant (dabigatran) but has not yet been specifically validated in the
345 elderly with VTE. Third, as we included patients who received anticoagulation
346 treatment with VKAs only, patients with cancer who may receive extended treatment
347 with low-molecular-weight heparin rather than with VKAs may be underrepresented
348 in our study. In addition, we included only surviving patients who were still under
349 VKAs at 3 months following the index VTE, which may further explain the lower

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

370 In conclusion, our findings indicate that, with the potential exception of the
371 Seiler score, existing bleeding risk scores do not have sufficient predictive accuracy
372 and discriminative power to identify elderly patients with VTE who are at high risk of
373 bleeding during extended treatment with VKAs. Thus, these scores do not appear to
374 be useful for identifying high-risk patients with VTE who are unsuitable candidates for
375 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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389 **REFERENCES**

390 1. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic Therapy for VTE Disease:
391 CHEST Guideline and Expert Panel Report. Chest. 2016;149(2):315-52
392 2. Linkins LA, Choi PT, Douketis JD. Clinical impact of bleeding in patients taking
393 oral anticoagulant therapy for venous thromboembolism: a meta-analysis. Ann Intern
394 Med. 2003;139(11):893-900
395 3. Spencer FA, Gore JM, Lessard D, et al. Venous thromboembolism in the
396 elderly. A community-based perspective. Thromb Haemost. 2008;100(5):780-8
397 4. Di Minno MN, Ambrosino P, Dentali F. Safety of warfarin in "high-risk"
398 populations: A meta-analysis of randomized and controlled trials. Thromb Res.
399 2017;150:1-7
400 5. Klok FA, Kooiman J, Huisman MV, Konstantinides S, Lankeit M. Predicting
401 anticoagulant-related bleeding in patients with venous thromboembolism: a clinically
402 oriented review. Eur Respir J. 2015;45(1):201-10
403 6. Klok FA, Hosel V, Clemens A, et al. Prediction of bleeding events in patients
404 with venous thromboembolism on stable anticoagulation treatment. Eur Respir J.
405 2016;48(5):1369-76
406 7. Seiler E, Limacher A, Mean M, et al. Derivation and validation of a novel
407 bleeding risk score for elderly patients with venous thromboembolism on extended
408 anticoagulation. Thromb Haemost. 2017;117(10):1930-6
409 8. Kuijer PM, Hutten BA, Prins MH, Buller HR. Prediction of the risk of bleeding
410 during anticoagulant treatment for venous thromboembolism. Arch Intern Med.
411 1999;159(5):457-60
412 9. Kearon C, Ginsberg JS, Kovacs MJ, et al. Comparison of low-intensity
413 warfarin therapy with conventional-intensity warfarin therapy for long-term prevention
414 of recurrent venous thromboembolism. N Engl J Med. 2003;349(7):631-9

415 10. Ruiz-Gimenez N, Suarez C, Gonzalez R, et al. Predictive variables for major
416 bleeding events in patients presenting with documented acute venous
417 thromboembolism. Findings from the RIETE Registry. Thromb Haemost.
418 2008;100(1):26-31
419 11. Landefeld CS, Goldman L. Major bleeding in outpatients treated with warfarin:
420 incidence and prediction by factors known at the start of outpatient therapy. Am J
421 Med. 1989;87(2):144-52
422 12. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-
423 friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with
424 atrial fibrillation: the Euro Heart Survey. Chest. 2010;138(5):1093-100
425 13. Gage BF, Yan Y, Milligan PE, et al. Clinical classification schemes for
426 predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF).
427 Am Heart J. 2006;151(3):713-9
428 14. Fang MC, Go AS, Chang Y, et al. A new risk scheme to predict warfarin-
429 associated hemorrhage: The ATRIA (Anticoagulation and Risk Factors in Atrial
430 Fibrillation) Study. J Am Coll Cardiol. 2011;58(4):395-401
431 15. Beyth RJ, Quinn LM, Landefeld CS. Prospective evaluation of an index for
432 predicting the risk of major bleeding in outpatients treated with warfarin. Am J Med.
433 1998;105(2):91-9
434 16. Tagalakis V, Patenaude V, Kahn SR, Suissa S. Incidence of and mortality
435 from venous thromboembolism in a real-world population: the Q-VTE Study Cohort.
436 Am J Med. 2013;126(9):832 e13-21
437 17. Mean M, Righini M, Jaeger K, et al. The Swiss cohort of elderly patients with
438 venous thromboembolism (SWITCO65+): rationale and methodology. J Thromb
439 Thrombolysis. 2013;36(4):475-83

440 18. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE
441 disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American
442 College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest.
443 2012;141(2 Suppl):e419S-e96S
444 19. Besarab A, Bolton WK, Browne JK, et al. The effects of normal as compared
445 with low hematocrit values in patients with cardiac disease who are receiving
446 hemodialysis and epoetin. N Engl J Med. 1998;339(9):584-90
447 20. Kampfen P, Mean M, Limacher A, et al. Risk of falls and bleeding in elderly
448 patients with acute venous thromboembolism. J Intern Med. 2014;276(4):378-86
449 21. Rosendaal FR, Cannegieter SC, van der Meer FJ, Briet E. A method to
450 determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost.
451 1993;69(3):236-9
452 22. Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the
453 Scientific and Standardization Committee of the International Society on Thrombosis
454 and Haemostasis. Definition of major bleeding in clinical investigations of
455 antihemostatic medicinal products in non-surgical patients. J Thromb Haemost.
456 2005;3(4):692-4
457 23. Scherz N, Mean M, Limacher A, et al. Prospective, multicenter validation of
458 prediction scores for major bleeding in elderly patients with venous
459 thromboembolism. J Thromb Haemost. 2013;11(3):435-43
460 24. Jakobsson C, Jimenez D, Gomez V, Zamarro C, Mean M, Aujesky D.
461 Validation of a clinical algorithm to identify low-risk patients with pulmonary
462 embolism. J Thromb Haemost. 2010;8(6):1242-7
463 25. Vickers AJ, Elkin EB. Decision curve analysis: a novel method for evaluating
464 prediction models. Med Decis Making. 2006;26(6):565-74

465 26. Jaeschke R, Guyatt GH, Sackett DL. Users' guides to the medical literature.
466 III. How to use an article about a diagnostic test. B. What are the results and will they
467 help me in caring for my patients? The Evidence-Based Medicine Working Group.
468 JAMA. 1994;271(9):703-7
469 27. Poli D, Antonucci E, Testa S, et al. The predictive ability of bleeding risk
470 stratification models in very old patients on vitamin K antagonist treatment for venous
471 thromboembolism: results of the prospective collaborative EPICA study. J Thromb
472 Haemost. 2013;11(6):1053-8
473 28. Donze J, Rodondi N, Waeber G, Monney P, Cornuz J, Aujesky D. Scores to
474 predict major bleeding risk during oral anticoagulation therapy: a prospective
475 validation study. Am J Med. 2012;125(11):1095-102
476 29. Jaspers Focks J, van Vugt SP, Albers-Akkers MT, et al. Low performance of
477 bleeding risk models in the very elderly with atrial fibrillation using vitamin K
478 antagonists. J Thromb Haemost. 2016;14(9):1715-24
479 30. Geldhof V, Vandenbriele C, Verhamme P, Vanassche T. Venous
480 thromboembolism in the elderly: efficacy and safety of non-VKA oral anticoagulants.
481 Thrombosis journal. 2014;12:21
482 31. Agnelli G, Buller HR, Cohen A, et al. Apixaban for extended treatment of
483 venous thromboembolism. N Engl J Med. 2013;368(8):699-708
484 32. Weitz JI, Lensing AWA, Prins MH, et al. Rivaroxaban or Aspirin for Extended
485 Treatment of Venous Thromboembolism. N Engl J Med. 2017;376(13):1211-22
486 33. Riva N, Bellesini M, Di Minno MN, et al. Poor predictive value of contemporary
487 bleeding risk scores during long-term treatment of venous thromboembolism. A
488 multicentre retrospective cohort study. Thromb Haemost. 2014;112(3):511-21
489 34. Mai V, Guay CA, Perreault L, et al. Extended Anticoagulation for VTE: A
490 Systematic Review and Meta-Analysis. Chest. 2019;155(6):1199-216

491 35. Aujesky D, Obrosky DS, Stone RA, et al. Derivation and validation of a
492 prognostic model for pulmonary embolism. Am J Respir Crit Care Med.
493 2005;172(8):1041-6
494 36. Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk
495 patients with community-acquired pneumonia. N Engl J Med. 1997;336(4):243-50
496

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 ICD-9-CM codes	Low risk	0-1 points
	b. 1 604	Ethanol abuse	1		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