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Novel Bleeding Risk Score for Patients with Atrial Fibrillation on Oral Anticoagulants, including Direct Oral Anticoagulants

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1 **Essentials:**

- 2 - Most current bleeding risk prediction tools for patients with atrial fibrillation (AF) and oral
3 anticoagulants are not designed for patients on direct oral anticoagulants (DOAC), but
4 DOACs have become a more and more popular choice of anticoagulant in AF patients.
5 - We present a new bleeding risk score derived from a prospective, population-based
6 cohort of AF-patients with predominantly DOAC users.
7 - Our score accurately identifies patients at low or high risk of bleeding after one year.-
8 After further external validation, this score will help the clinician to balance the risk of
9 bleeding in AF patients, including DOAC users.

1

2 **Abstract:**

3 **Objective**

4 Balancing bleeding risk and stroke risk in patients with atrial fibrillation (AF) is a common
5 challenge. Though several bleeding risk scores exist, most have not included patients on
6 direct oral anticoagulants (DOAC). We aimed at developing a novel bleeding risk score
7 for patients with AF on oral anticoagulants (OAC) including both, vitamin K antagonists
8 (VKA) and DOACs.

9 **Methods**

10 We included patients with AF on OAC from a prospective multicentre cohort study in
11 Switzerland (SWISS-AF). The outcome was time to first bleeding. Bleeding events were
12 defined as major or clinically relevant non-major bleeding. We used backward elimination
13 to identify bleeding risk variables. We derived the score using a point score system based
14 on the beta coefficients from the multivariable model. We used the Brier score for model
15 calibration (<0.25 indicating good calibration), and Harrel's c-statistics for model
16 discrimination. .

17 **Results**

18 We included 2,147 patients with AF on OAC (72.5% male, mean age 73.4 ± 8.2 years), of
19 whom 1209 (56.3%) took DOAC. After a follow-up of totally 4.4. years, a total of 255
20 (11.9%) bleeding events occurred. After backward elimination, age >75 years, history of
21 cancer, prior major haemorrhage and arterial hypertension remained in the final
22 prediction model. The Brier score was 0.23 (95% CI 0.19- 0.27), the c-statistics at 12
23 months was 0.71 (95%CI 0.63 - 0.80).

24 **Conclusion**

25 In this prospective cohort study of AF patients and predominantly DOAC users, we
26 successfully derived a bleeding risk prediction model with good calibration and
27 discrimination.

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29

30 **Word count Abstract: 243**

- 1 **Keywords:** atrial fibrillation, bleeding risk, oral anticoagulants, direct oral anticoagulants,
2 SWISS-AF

1 Introduction:

2 Atrial fibrillation (AF), the most common arrhythmia, is associated with increased risk for
3 cardiac thromboembolism [1]. AF is present in about 1-2% of the population [2] and
4 associated with increased risk for cardiac thromboembolism [1], causing almost a third of
5 strokes [3]. Thromboembolism and stroke risk can be greatly reduced if oral
6 anticoagulants (OAC, including both VKA and DOAC) are administered, but this
7 treatment increases bleeding risk [4] [5]. Balancing bleeding risk against stroke risk for
8 each patient is essential, but the clinical tools designed to predict a patient's risk of
9 bleeding and thromboembolism are sub-optimal [3].

10 Bleeding risk scores like HAS-BLED [6], HEMORR₂HAGES [7], ATRIA [8] and ORBIT [9]
11 were designed to identify patients at high risk of bleeding and to help doctors decide
12 which patients can safely be given anticoagulants, but they showed limited predictive
13 scores with c-statistics ranging from 0,54 to 0,61 [10] [11]. A few years ago, direct oral
14 anticoagulants (DOAC) were introduced and have proved as effective as VKA in
15 preventing cardiac thromboembolism and stroke in AF patients, with lower bleeding risk.
16 Though clinicians increasingly use DOAC in AF patients to prevent stroke and systemic
17 embolisms [12, 13], all but two studies included very few DOAC users in their bleeding
18 prediction models. The first of these studies, published in 2015, derived its ORBIT score
19 based on patients on Rivaroxaban in a large randomised trial (Rocket-AF) with strict
20 inclusion and exclusion criteria and only patients who received a single DOAC [9]. The
21 other, a 2018 study, developed its score from a Norwegian patient registry [14] which
22 included patients on all types of DOAC, but their data source lacked prospective
23 evaluation of the main outcome.

24 Given the limitations of existing scores and the need for better prediction tools for
25 patients on DOAC, we developed and internally validated a novel clinical prediction score
26 for patients with AF who were treated with either VKA or DOAC based on data from a
27 prospective cohort study with adjudicated clinical outcomes.

1 **Methods**

2 We developed and internally validated a prognostic score for predicting bleeding in
3 patients with AF under OAC treatment (VKA or DOAC) from the Swiss-Atrial Fibrillation
4 (SWISS-AF) cohort study. SWISS-AF is a multicentre Swiss cohort study that includes
5 patients aged ≥ 65 years with documented AF (paroxysmal, persistent or permanent),
6 already described in detail [15]. The SWISS-AF study was approved by all local ethics
7 committees. (PB_2016-00793, for Bern, "Ethikkommission Nordwest- und
8 Zentralschweiz" EKNZ 2014-067. KEK-BE Nr. 032/14); our study required no further
9 review by an ethics committee. We excluded data from patients who were unable to
10 provide informed consent, suffered only short episodes of reversible forms of AF, had
11 had recent surgery (≤ 3 weeks prior to baseline), or were missing follow-up information.
12 We also excluded patients who were not under OAC (VKA or DOAC) at baseline.

13 This study adheres to the transparent reporting of a multivariable prediction model for
14 individual prognosis or diagnosis (TRIPOD) statement [16]. We internally validated the
15 model we developed by applying dedicated methods in the development population.

16 17 Definition and assessment of outcomes

18 Our primary outcome was the time to major or clinically relevant non-major bleeding for
19 up to 48 months after study inclusion. To better compare our model's scores to other
20 bleeding risk scores, we focused on the score for prediction after one year. Our
21 secondary endpoint analyses assessed the predictive accuracy of the score for major-,
22 intracranial and clinically relevant non-major bleeding respectively. We drew our definition
23 of major bleeding from the International Society on Thrombosis and Haemostasis:
24 clinically overt fatal bleeding or bleeding that reduced haemoglobin level of ≥ 20 g/L within
25 seven days and required transfusion of at least two units of red blood cells, or
26 symptomatic bleeding in a critical area or organ (intracranial, intraspinal, intraocular,
27 pericardial, intra-auricular, intramuscular with compartment syndrome, retroperitoneal)
28 [17]. Clinically relevant non-major bleeding was defined as bleeding that was not major,
29 but was clinically overt and led to hospitalisation, change of antithrombotic therapy, or
30 necessitated a medical or surgical intervention [15].

1 At each yearly study visit, patients were asked about bleeding events and their medical
2 history was updated. If a patient had a bleeding event, local study nurses collected all
3 relevant source documents, e.g. hospital reports, laboratory results, operational reports.
4 Local senior physicians then confirmed events and adjudicated the outcome based on
5 the criteria for bleeding.

6 Statistical analysis

7 We calculated the proportion (%) and mean ($\pm$ Standard Deviation (SD)) for all potential
8 bleeding predictor candidates previously identified by literature search (s. Table 1) for
9 continuous and dichotomous variables respectively. Those variables were tested in
10 univariable models for their association with the main bleeding endpoint. We used a ratio-
11 likelihood-test to check for linear association of continuous variables with the combined
12 bleeding endpoint. To make it easier for clinicians to use the score, we chose the median
13 for age as category cut-off and created our categories based on quartiles for variables
14 that did not show linear association with the endpoint but had a normal distribution.
15 We analysed time to first major or clinically relevant non-major bleeding event; non-
16 bleeding-related deaths were a competing event. To do this, we used a maximum
17 likelihood competing risk regression model, according to Fine and Gray's method [18]
18 entering those variables associated with $p < 0.2$ in univariable analyses. We used
19 backward elimination to eliminate variables with a p -value > 0.05 , so we could identify the
20 remaining variables in the final prediction model. For variables with missing baseline
21 data, we used multiple imputations [19] based on all available full baseline datasets. We
22 derived the risk score based on a point score system; we calculated the points we
23 assigned to the predictors identified in the final model, by dividing each β -coefficient by
24 the lowest β -coefficient and then rounding the result to the nearest integer [20]. We
25 divided patients into three categories of increasing bleeding risk (low, moderate, high).
26 There are no generally accepted cut-offs for low or high risk categories, so we decided to
27 use categories similar to those used by other scores: $< 3\%$ for low bleeding risk; $> 6.4\%$ as
28 the cut-off for high bleeding risk [21]. We calculated incidence rates with 95% confidence
29 intervals (CI) for bleeding in each category, based on the observed bleeding events. We
30 also applied the risk score to patients under either VKA or DOAC at baseline.

1 We assessed the overall discriminatory ability of the model and of the risk score with
2 Harrel's C-statistic (summarised as the area under receiver operating characteristic curve
3 [AUC ROC]) with 95% CI. The score's predictive accuracy was assessed at 6, 12, 24, 36
4 and 48 months as well as after the maximum follow-up (4.4 years). Model calibration was
5 assessed with the Brier score[22], with <0.25 deemed as good calibration. We also used
6 the remaining predictors to calculate the ratio of expected/observed values.
7 For internal model and score validation, we used bootstrapping methods [23]. We
8 performed 500 bootstrap cycles in the original sample, resampling the same number of
9 patients. First, we assessed apparent overall model discrimination within 500 bootstrap
10 cycles. Next, we calculated shrinkage and optimism adjusted c- statistic for the score.
11
12 We used the same methods described above to assess c-statistics over time for existing
13 bleeding risk scores designed for patients with AF (HAS-BLED [6], ATRIA [8], ORBIT [9])
14 and a new prediction score predicting bleeding in AF patients taking only DOACs [14].
15 The scores were applied within our cohort for major and clinically relevant bleeding. We
16 compared the performance of our score with previously existing scores' performances at
17 12 months and 4.4. years by using DeLong and Clarke's method [24]. To make our
18 results more comparable, we focused on the score's predictive performance at twelve
19 months.
20 STATA Version 16.0. (Stata Corporation, College Station, Texas) was used for all
21 statistical analyses.

Results

The SWISS-AF Cohort study included 2,415 patients with AF; of these 37 were lost to follow-up and 230 did not take OAC (VKA/DOAC) at baseline (supplementary Figure 1), which left 2,147 patients on OAC. Patients' baseline characteristics by bleeding status are presented in Table 1. Mean age was 73.4 (standard deviation (SD) $\pm$ 8.2 years); 72.5% of our study population were men. During a mean follow-up of 2.1 years (maximum 4.4 years), there were 255 bleeding events, including 107 (42.0%) major bleeding events, of which 13 (12.2%) were intracranial. After twelve months, 25 major and clinically relevant bleedings occurred (2 intracranial), resulting in a 1.16% absolute bleeding risk at one year. The annual bleeding rate per person year was 5.77% (95%CI 5.11%-6.53%) and 0.29% (95%CI 0.17%-0.51%) for intracranial bleedings.

Potential predictors

From the literature we identified 28 risk factors with reported independent association with bleeding (supplementary Table 1). The SWISS-AF study collected most of those variables at baseline. Table 2 shows the final predictors we entered into the model. Unlike earlier prediction models, ours did not find history of diabetes mellitus was a risk factor in the univariate analysis, so we did not consider it as a predictor for the combined bleeding endpoint.

After a test for linearity, no continuous variables showed a linear association with the combined endpoint, so all continuous variables were categorized. After multivariable competing risk analysis and stepwise backward selection, age $\geq$ 75 years, history of cancer, arterial hypertension, and history of major bleeding were retained in the final prediction model. In a sensitivity analysis, adding NSAR, sex and use of aspirin at baseline in the multivariable model and repeating the multivariable stepwise backwards analysis, the same four variables were identified.

Score derivation, model calibration and discrimination

We assigned point scores based on the beta-coefficient from the prediction model using a point score system (Table 3) [20]. The Brier score was 0.23 (95% CI 0.19-0.27), showing that the model was well calibrated; expected/observed probabilities were 1.02 at

1 12 months, 0.99 at 24 months and 0.99 and 36 months (supplementary Figure 1-3). After
2 building the score from the prediction model's beta coefficients, the c-statistic for the
3 score was 0.71 (95%CI 0.63-0.80) at twelve months. The predictive ability of the score
4 decreased over time, from 0.66 (95%CI 0.61-0.72) at 24 months to 0.64 (95%CI 0.60-
5 0.68) at 36 and 48 months). For the whole follow-up period, the score's c-statistic was
6 0.62 (95%CI 0.59-0.65) (Table 5).

7 When we stratified bleeding risk into three categories (low, moderate, high), most
8 patients (n=1,579, 73.5%) were classed as moderate; there were 5.9 bleeding events
9 (95%CI 5.1-6.8) per 100 patient years. Overall, 394 (18.4%) of patients were at low risk
10 of bleeding (2.5 bleedings per 100 years) and 174 (8.1%) were at high risk (12.9 per 100
11 patient years) (Table 4).

12 Validation

13 The performance of the score after internal validation showed an area under the curve of
14 0.62 (95%CI 0.59-0.66) taking into account the entire follow- up period. These results
15 were similar to those from the derivation. Optimism-adjusted c-statistic was 0.64 for the
16 score.

17 Comparison with existing bleeding risk scores

18 We compared predictive performance at twelve months for existing bleeding risk scores
19 and found the prediction accuracy of the ATRIA and Rutherford scores was very similar
20 to ours. Our score was more accurate than HAS-BLED and ORBIT scores after 12
21 months (Table 5), but differences did not show statistical significance (Our score 0.71
22 [95%CI 0.63-0.80] vs. HAS-BLED 0.63 [95%CI 0.52-0.74] p=0.28, Our score vs. ORBIT
23 0.69 [95%CI 0.60-0.78] p=0.76, s.Table 2)

24 Considering the full follow-up period, all scores predicted bleeding risk about equally well
25 (ATRIA 0.60 (95% CI 0.57-0.64) HAS-BLED 0.60 (95% CI 0.56-0.63) ORBIT 0.59 (95%
26 CI 0.55-0.62) and the score from Rutherford et.al. 0.62 (95% CI 0.58-0.66) (Table 5,
27 s.Table 2).

28 Secondary analyses

1 The discriminative ability of our score for major bleeding was 0.67 (95% CI 0.53-0.81) up
2 to one year, ranging to 0.62 (95%CI 0.57-0.68) after the whole follow-up period. C-
3 statistics for clinically relevant non-major bleeding was 0.60 (95%CI, 0.54- 0.66) up to
4 twelve months and 0.61 (95%CI 0.56-0.65) after the entire follow-up period.

5 For intracranial bleeding, the c- statistics was 0.63 (95%CI 0.51 -0.75) for the entire
6 duration (4.4 years); analyses were limited by the low number of such events (n= 2 after
7 12 months and n=13 for the overall follow-up).When applied to patients treated with only
8 DOACs, the c-statistic for our score was 0.73 (95% CI 0.59 - 0.87) at twelve months, and
9 was 0.64 (95%CI 0.59-0.69) for the whole follow-up period. The c-statistic for the score
10 that estimated combined bleeding endpoint for patients only given VKA was 0.58 (0.29 to
11 0.87) after 12 months and 0.59 (95%CI 0.54-0.64) after the entire follow-up period.

1 Discussion:

2 Based on a Swiss multi-centre prospective cohort study, we developed a clinical
3 prediction model with good calibration and good discrimination for major and clinically
4 relevant moderate-to-minor bleeding in patients with AF who took oral anticoagulants
5 (VKA or DOAC); c-statistics ranged from 0.76 at 6 months to 0.62 at 4.4 years. Over 50%
6 of patients in the cohort were treated with various DOAC. To our knowledge, this is the
7 first bleeding prediction model from a prospective cohort study including a considerably
8 high proportion of DOAC in patients with AF.

9 When we compared the performance of established scores in our cohort, our results
10 aligned with those in the literature [11]. Only the Rutherford et al. and ORBIT bleeding
11 risk prediction scores were derived to predict bleeding in patients on DOAC; the
12 Rutherford-score was derived to predict bleeding in patients who received DOAC only,
13 while ORBIT was developed to predict bleeding in patients on Rivaroxaban and VKA. Our
14 score included patients who used VKA and varying DOAC, so it may be more
15 representative for patients with AF seen in clinical practice. Our and Rutherford et al's
16 scores made similarly accurate predictions after one year when we applied them to our
17 cohort: c-statistics were 0.71 for our score (95% CI 0.63 to 0.80), and 0.72 for Rutherford
18 (95% CI 0.63-0.82) after one year; for the whole follow-up period, the scores were almost
19 the same (ours was 0.62, 95%CI 0.59-0.65; Rutherford was 0.62, 95%CI 0.58-0.66) [14].
20 But the Rutherford score was derived from a retrospective population study, which is not
21 a recommended method for deriving a prediction model [25]. A study from a Danish
22 registry examined the predictive accuracy of the HAS-BLED, ATRIA and ORBIT scores
23 for major bleeding after one year in patients with AF who used DOAC; their study found
24 comparable c-statistics to we did for overall follow-up (ATRIA 0.59, 95% CI 0.57-0.60;
25 HAS-BLED 0.58, 95%CI 0.57-0.59; ORBIT 0.61, 95% CI 0.59-0.62) [26].

26 Our score better predicted bleeding for patients only taking DOACs which suggests that
27 DOAC's and VKA's different pharmacological effects require that we assess patients who
28 take each of these drugs differently. In our cohort, patients using VKA were older and
29 were suffering more from arterial hypertension and chronic kidney disease. More
30 bleedings occurred in VKA users (13% of VKA users had major and clinically relevant

non-major bleeding within the entire follow up and bleedings occurred in 10% of DOAC users). These findings go well in line with previous trials, showing difference between VKA and DOAC. [27] We did not derive a prediction model for the patients who only used DOAC because our statistical power was too limited.

Most scores were derived to predict major bleeding over one or two years. Our score assessed a combined bleeding endpoint up to 4.4 years of follow-up. Over the long term (after 6.5 years), HAS BLED's c-statistic was 0.58 for major bleeding [28]. A study that evaluated TIMI-significant bleedings (defined as major or minor) and bleeding requiring medical attention in patients using OAC and antiplatelet therapy, with a 3-year follow-up found AUC was 0.62 for HAS-BLED and 0.61 for ORBIT [29]. As in our study, the occurrence of more confounding variables, like starting to take aspirin, age, and comorbid conditions, might account for the decrease in discriminative power over time.

Although c-statistics are not excellent and do decrease over time, our score may better identify patients at the extremes of low and high risk of bleeding; if so, it could help clinicians weigh the risks and benefits of oral anticoagulants.

Similar to current AF guidelines [30] not suggesting to withhold OAC for patients with a high risk of bleeding, our study cannot answer the question when to withhold OAC treatment. Current AF guidelines [30] suggest the HAS-BLED score as a risk assessment tool to try to reduce bleeding risk by treating obvious risk factors (e.g. hypertension).

Strengths and limitations

An important strength of this study was that the analyzed data were from a large, prospective cohort study with broad inclusion criteria and thus broad external validity. By combining a literature review with a prospective analysis of associated risk factors, we found good supported predictors for a stable model. Another strength of our study is the validation of known bleeding risk scores in this cohort of predominantly DOAC users. This study had several limitations to consider. The most important limitation is the lack of external validation. We used bootstrapping methods for internal validation as a split sample method would not have allowed for sufficient power to derive the score. In

1 contrast to the HAS-BLED score, our score mostly consists of variables for risk factors
2 that cannot be modified to reduce bleeding risk.
3 However our score may assist with the identification of patients who may benefit from
4 more frequent clinical monitoring (e.g. to assess for signs of occult bleeding or the need
5 for dose adaptation of DOACs in case of concomitant renal dysfunction). Another
6 limitation is the definition of history of cancer, which encompassed active or cured cancer
7 of any type. A definition limited to active cancer might have led to a stronger association
8 between cancer and bleeding, (potentially “non-differential” misclassification). However,
9 even with this broad definition of cancer, it remains an independent predictor in our score.
10 Also, the patients in this bleeding risk model were mostly elderly. Therefore the predictive
11 ability in younger patients remains unknown.

12 Conclusion

13 In this prospective cohort study of patients with AF we derived a bleeding risk prediction
14 model with good calibration and discrimination at one year. Our score identifies patients
15 at low risk of bleeding who can safely use and benefit from anticoagulants, and those at
16 high risk, whose risk of anticoagulation should be carefully evaluated after controlling for
17 all known bleeding risk factors, but it should be externally validated before being
18 implemented into practice.
19

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18 **Authors contributions:**

19 Conception and design of the study: MF, JD, DS, RL, DC, DA, NR

20 Acquisition of data: LA, MF, DS, CF, LR, UF, SA, GM, JS, DS, PA, RK, MS, MK, LHB, JB, SO,
21 DC, DA, NR

22 Analysis & interpretation of data: LA, MF, LS, CDG, JD, CB, DA, NR

23 Drafting of the article: LA, MF, CGD, CB, NR

24 Acquisition of funding: DS, JD, MR

25 Critical revision for scientific content: all listed authors

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1 **References:**

- 2 1 Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the
3 Framingham Study. *Stroke*. 1991; **22**: 983-8.
- 4 2 Rodriguez-Manero M, Lopez-Pardo E, Cordero-Fort A, Martinez-Sande JL, Pena-Gil C, Platas JN,
5 Garcia-Seara J, Mazon P, Varela-Roman A, Garcia-Acuna JM, Gonzalez-Juanatey JR. Prevalence and
6 outcomes of atrial fibrillation in a European healthcare area gained through the processing of a health
7 information technology system. *Revista portuguesa de cardiologia : orgao oficial da Sociedade Portuguesa*
8 *de Cardiologia = Portuguese journal of cardiology : an official journal of the Portuguese Society of*
9 *Cardiology*. 2019; **38**: 21-9. 10.1016/j.repc.2018.06.008.
- 10 3 Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel
11 H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, Agewall
12 S, Camm J, Baron Esquivias G, Budts W, Carerj S, Casselman F, Coca A, De Caterina R, Devereux S, Dobrev
13 D, Ferro JM, Filippatos G, Fitzsimons D, Gorennek B, Guenoun M, Hohnloser SH, Kolh P, Lip GY, Manolis A,
14 McMurray J, Ponikowski P, Rosenehek R, Ruschitzka F, Savelieva I, Sharma S, Suwalski P, Tamargo JL, Taylor
15 CJ, Van Gelder IC, Voors AA, Windecker S, Zamorano JL, Zeppenfeld K. 2016 ESC Guidelines for the
16 management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016; **37**: 2893-962.
17 10.1093/eurheartj/ehw210.
- 18 4 Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of
19 pooled data from five randomized controlled trials. *Archives of internal medicine*. 1994; **154**: 1449-57.
- 20 5 van Walraven C, Hart RG, Singer DE, Laupacis A, Connolly S, Petersen P, Koudstaal PJ, Chang Y,
21 Hellemons B. Oral anticoagulants vs aspirin in nonvalvular atrial fibrillation: an individual patient meta-
22 analysis. *Jama*. 2002; **288**: 2441-8.
- 23 6 Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-
24 BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey.
25 *Chest*. 2010; **138**: 1093-100. 10.1378/chest.10-0134.
- 26 7 Gage BF, Yan Y, Milligan PE, Waterman AD, Culverhouse R, Rich MW, Radford MJ. Clinical
27 classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation
28 (NRAF). *American heart journal*. 2006; **151**: 713-9. 10.1016/j.ahj.2005.04.017.
- 29 8 Fang MC, Go AS, Chang Y, Borowsky LH, Pomernacki NK, Udaltsova N, Singer DE. A new risk
30 scheme to predict warfarin-associated hemorrhage: The ATRIA (Anticoagulation and Risk Factors in Atrial
31 Fibrillation) Study. *Journal of the American College of Cardiology*. 2011; **58**: 395-401.
32 10.1016/j.jacc.2011.03.031.

- 1 9 O'Brien EC, Simon DN, Thomas LE, Hylek EM, Gersh BJ, Ansell JE, Kowey PR, Mahaffey KW, Chang
2 P, Fonarow GC, Pencina MJ, Piccini JP, Peterson ED. The ORBIT bleeding score: a simple bedside score to
3 assess bleeding risk in atrial fibrillation. *Eur Heart J*. 2015; **36**: 3258-64. 10.1093/eurheartj/ehv476.
- 4 10 Donze J, Rodondi N, Waeber G, Monney P, Cornuz J, Aujesky D. Scores to predict major bleeding
5 risk during oral anticoagulation therapy: a prospective validation study. *The American journal of medicine*.
6 2012; **125**: 1095-102. 10.1016/j.amjmed.2012.04.005.
- 7 11 Apostolakis S, Lane DA, Guo Y, Buller H, Lip GY. Performance of the HEMORR(2)HAGES, ATRIA, and
8 HAS-BLED bleeding risk-prediction scores in patients with atrial fibrillation undergoing anticoagulation:
9 the AMADEUS (evaluating the use of SR34006 compared to warfarin or acenocoumarol in patients with
10 atrial fibrillation) study. *Journal of the American College of Cardiology*. 2012; **60**: 861-7.
11 10.1016/j.jacc.2012.06.019.
- 12 12 Engelberger RP, Noll G, Schmidt D, Alatri A, Frei B, Kaiser WE, Kucher N. Initiation of rivaroxaban
13 in patients with nonvalvular atrial fibrillation at the primary care level: the Swiss Therapy in Atrial
14 Fibrillation for the Regulation of Coagulation (STAR) Study. *European journal of internal medicine*. 2015;
15 **26**: 508-14. 10.1016/j.ejim.2015.04.014.
- 16 13 Olesen JB, Sorensen R, Hansen ML, Lamberts M, Weeke P, Mikkelsen AP, Kober L, Gislason GH,
17 Torp-Pedersen C, Fosbol EL. Non-vitamin K antagonist oral anticoagulation agents in anticoagulant naive
18 atrial fibrillation patients: Danish nationwide descriptive data 2011-2013. *Europace : European pacing,
19 arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias,
20 and cardiac cellular electrophysiology of the European Society of Cardiology*. 2015; **17**: 187-93.
21 10.1093/europace/euu225.
- 22 14 Rutherford OW, Jonasson C, Ghanima W, Holst R, Halvorsen S. New score for assessing bleeding
23 risk in patients with atrial fibrillation treated with NOACs. *Open heart*. 2018; **5**: e000931.
24 10.1136/openhrt-2018-000931.
- 25 15 Conen D, Rodondi N, Mueller A, Beer J, Auricchio A, Ammann P, Hayoz D, Kobza R, Moschovitis G,
26 Shah D, Schlaepfer J, Novak J, di Valentino M, Erne P, Sticherling C, Bonati L, Ehret G, Roten L, Fischer U,
27 Monsch A, Stippich C, Wuerfel J, Schwenkglenks M, Kuehne M, Osswald S. Design of the Swiss Atrial
28 Fibrillation Cohort Study (Swiss-AF): structural brain damage and cognitive decline among patients with
29 atrial fibrillation. *Swiss Med Wkly*. 2017; **147**: w14467. 10.4414/smw.2017.14467.
- 30 16 Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent Reporting of a multivariable prediction
31 model for Individual Prognosis or Diagnosis (TRIPOD): the TRIPOD statement. *Ann Intern Med*. 2015; **162**:
32 55-63. 10.7326/M14-0697.

- 1 17 Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the S, Standardization
2 Committee of the International Society on T, Haemostasis. Definition of major bleeding in clinical
3 investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost*. 2005; **3**:
4 692-4. 10.1111/j.1538-7836.2005.01204.x.
- 5 18 Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *Journal*
6 *of the American Statistical Association* 1999: 496-509.
- 7 19 Moons KG, Donders RA, Stijnen T, Harrell FE, Jr. Using the outcome for imputation of missing
8 predictor values was preferred. *Journal of clinical epidemiology*. 2006; **59**: 1092-101.
9 10.1016/j.jclinepi.2006.01.009.
- 10 20 Bonnett LJ, Snell KIE, Collins GS, Riley RD. Guide to presenting clinical prediction models for use in
11 clinical settings. *Bmj*. 2019; **365**: l737. 10.1136/bmj.l737.
- 12 21 Seiler E, Limacher A, Mean M, Beer HJ, Osterwalder J, Frauchiger B, Righini M, Aschwanden M,
13 Matter CM, Banyai M, Kucher N, Staub D, Lammle B, Rodondi N, Squizzato A, Aujesky D. Derivation and
14 validation of a novel bleeding risk score for elderly patients with venous thromboembolism on extended
15 anticoagulation. *Thrombosis and haemostasis*. 2017; **117**: 1930-6. 10.1160/TH17-03-0162.
- 16 22 Brier G. Verification of forecasts expressed in terms of probability. *Monthly Weather Review*.
17 1950; **78**: 1-3.
- 18 23 Steyerberg EW, Harrell FE, Jr., Borsboom GJ, Eijkemans MJ, Vergouwe Y, Habbema JD. Internal
19 validation of predictive models: efficiency of some procedures for logistic regression analysis. *Journal of*
20 *clinical epidemiology*. 2001; **54**: 774-81. 10.1016/s0895-4356(01)00341-9.
- 21 24 DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated
22 receiver operating characteristic curves: a nonparametric approach. *Biometrics*. 1988; **44**: 837-45.
- 23 25 Moons KG, Kengne AP, Woodward M, Royston P, Vergouwe Y, Altman DG, Grobbee DE. Risk
24 prediction models: I. Development, internal validation, and assessing the incremental value of a new
25 (bio)marker. *Heart*. 2012; **98**: 683-90. 10.1136/heartjnl-2011-301246.
- 26 26 Lip GYH, Skjoth F, Nielsen PB, Kjaeldgaard JN, Larsen TB. The HAS-BLED, ATRIA, and ORBIT
27 Bleeding Scores in Atrial Fibrillation Patients Using Non-Vitamin K Antagonist Oral Anticoagulants. *The*
28 *American journal of medicine*. 2018; **131**: 574 e13- e27. 10.1016/j.amjmed.2017.11.046.
- 29 27 Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, Camm AJ, Weitz
30 JI, Lewis BS, Parkhomenko A, Yamashita T, Antman EM. Comparison of the efficacy and safety of new oral
31 anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials.
32 *Lancet*. 2014; **383**: 955-62. 10.1016/S0140-6736(13)62343-0.

- 1 28 Esteve-Pastor MA, Rivera-Caravaca JM, Roldan V, Vicente V, Valdes M, Marin F, Lip GYH. Long-
2 term bleeding risk prediction in 'real world' patients with atrial fibrillation: Comparison of the HAS-BLED
3 and ABC-Bleeding risk scores. The Murcia Atrial Fibrillation Project. *Thrombosis and haemostasis*. 2017;
4 **117**: 1848-58. 10.1160/TH17-07-0478.
- 5 29 Yoshida R, Ishii H, Morishima I, Tanaka A, Morita Y, Takagi K, Yoshioka N, Hirayama K, Iwakawa N,
6 Tashiro H, Kojima H, Mitsuda T, Hitora Y, Furusawa K, Tsuboi H, Murohara T. Performance of HAS-BLED,
7 ORBIT, PRECISE-DAPT, and PARIS risk score for predicting long-term bleeding events in patients taking an
8 oral anticoagulant undergoing percutaneous coronary intervention. *Journal of cardiology*. 2019; **73**: 479-
9 87. 10.1016/j.jjcc.2018.10.013.
- 10 30 Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomstrom-Lundqvist C, Boriani G, Castella M,
11 Dan GA, Dilaveris PE, Fauchier L, Filippatos G, Kalman JM, La Meir M, Lane DA, Lebeau JP, Lettino M, Lip
12 GYH, Pinto FJ, Thomas GN, Valgimigli M, Van Gelder IC, Van Putte BP, Watkins CL, Group ESCSD. 2020 ESC
13 Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the
14 European Association of Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2020. 10.1093/eurheartj/ehaa612.
- 15 31 Burger M, Bronstrup A, Pietrzik K. Derivation of tolerable upper alcohol intake levels in Germany:
16 a systematic review of risks and benefits of moderate alcohol consumption. *Preventive medicine*. 2004;
17 **39**: 111-27. 10.1016/j.ypmed.2003.11.011.

1 Tables and Figures:

2 Table 1: Baseline Characteristics

	All (n=2147)	Major & relevant Bleeding (n=255)	No Bleeding (n=1892)
¹ Age [years]	73.4 ± 8.2	73.1 ± 8.3	75.9 ± 8.2
Sex [%]			
Male	1556 (72.5)	1367 (72.3)	189 (74.12)
Female	591 (27.5)	525 (27.7)	66 (27.53)
Height [cm]	172.2 ± 9.0	172.1 ± 8.6	172.2 ± 9.0
Weight [kg]	82.6 ± 16.4	82.6 ± 16.4	82.6 ± 15.9
² Type of AF [%]			
Paroxysmal	919 (42.8)	106 (41.6)	813 (43.0)
Persistent	652 (30.4)	70 (27.5)	582 (30.8)
Permanent	576 (26.8)	79 (31.0)	497 (26.2)
Smoking [%]			
Active	145 (6.8%)	15 (5.88)	130 (6.88)
Former smoker	1062 (49.5)	118 (46.27)	944 (49.97)
Never smoker	937 (43.6%)	122 (47.84)	815 (43.14)
⁴ Type of VKA [%]			
Phenprocoumon	725 (33.8)	113 (44.3)	612 (32.4)
Acenocoumarol	213 (9.9)	13 (5.1)	200 (10.6)
⁴ DOAC [%]			
Rivaroxaban	886 (41.3)	88 (34.5)	798 (42.2)
Dabigatran	79 (3.7)	11 (4.3)	68 (3.6)
Apixaban	204 (9.5)	27 (10.6)	177 (9.4)
Edoxaban	40 (1.9)	3 (1.2)	37 (2.0)
⁵ Poor INR control [%]	89 (4.15)	13 (5.1)	76 (4.0)
⁶ Prior stroke/TIA [%]	443 (20.6)	67 (26.3)	376 (19.9)
Heart failure [%]	569 (26.5)	83 (32.6)	486 (25.7)
⁷ Hypertension [%]	1516 (70.6)	209 (82.0)	1307 (69.1)
⁸ Hemoglobin [g/L]	135.5 ± 19.1	131.6 ± 19.4	136.1 ± 19.0
⁸ Hematocrite [L/L]	40.4 ± 5.4	39.6 ± 5.4	40.6 ± 5.4
⁸ Thrombocytes [G/L]	223.4 ± 73.2	216.1 ± 71.4	224.4 ± 73.4
⁹ History of cancer [%]	339 (15.8)	54 (21.2)	285 (15.1)
Prior major haemorrhage [%]	48 (2.24)	10 (3.9)	38 (2.0)
Diabetes [%]	373 (17.4)	38 (14.9)	335 (17.7)

History of falls [%]	179 (8.3)	29 (11.4)	150 (7.9)
Prior gastric ulcer [%]	93 (4.3)	17 (6.7)	76 (4.0)
Coronary artery disease [%]	351 (16.4)	46 (18.0)	305 (16.1)
Other embolic events [%]	112 (5.2)	16 (6.3)	96 (5.1)
History of VTE [%]	205 (0.6)	23 (9.0)	182 (9.6)
Antiplatelet therapy [%]	340 (15.8)	46 (18.0)	294 (15.6)
Use of NSAID [%]	47 (2.2)	8 (3.1)	39 (2.1)
¹⁰ Use of PPI [%]	664 (30.9)	97 (38.0)	567 (30.0)
Peripheral arterial disease [%]	170 (7.9)	27 (10.6)	143 (7.6)
¹¹ Risky alcohol consumption [%]	87 (4.1)	10 (3.9)	77 (4.1)
¹² ALAT [U/L]	23.6 ± 10.8	23.0 ± 9.7	23.7 ± 10.9
¹³ Creatinine [μmol/L]	110.5 ± 51.6	119 ± 55.6	109 ± 51.0

1 Definition of variables:

2 ¹Age= age in years at study inclusion;

3 ²Type of AF paroxysmal= self-terminating AF lasting less than 7 days without need for
4 cardioversion, documented at least twice within 60months; persistent AF= AF that lasted 7 days
5 or longer and/or requiring cardioversion documented in the last 60 months by ECG or rhythm
6 monitoring devices; permanent AF: AF lasts permanently, cardioversion has failed or not been
7 attempted.

8 ³Smoking as assessed by self-report

9 ⁴Direct Oral anticoagulants: type of anticoagulant at baseline

10 ⁵Poor INR control= less than 30% if INR values in therapeutic range [21]

11 ⁶Prior Stroke/TIA= history of ischaemic or haemorrhagic stroke or TIA before study inclusion, self-
12 reported or from available medical documentation;

13 ⁷Hypertension: history of hypertension, self-reported or from available medical documentation, or
14 taking oral antihypertensives, controlled or uncontrolled

15 ⁸Hemoglobin, hematocrite and thrombocytes: measured within the last six months prior to study
16 inclusion

17 ⁹History of cancer: any active or cured cancer

1 ¹⁰ Use of proton pump inhibitors at baseline

2 ¹¹ Risky alcohol consumption: >1 standard glass/d (SG) for women, >2 SG/d for men [31]

3 ¹² ALAT: in U/L, measured at baseline

4 ¹³ Creatinine: in mmol/l, measured at baseline

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1 **Table 2: Selection of predictors after univariable and stepwise backward multivariable analysis**

Variable	Univariable			Multivariable analysis		
	Sub-Hazard Ratio	β -Coeff. (95% CI)	p-value	Sub-Hazard Ratio	β -Coeff. (95% CI)	p-value
Age ≥ 75	1.76 (1.38-2.25)	0.57 (0.32-0.81)	<0.001	1.61 (1.25-2.07)	0.48 (0.22; 0.73)	<0.001
Hypertension	1.79 (1.30-2.46)	0.58 (0.26; 0.90)	<0.001	1.62 (1.17-2.25)	0.48 (0.16; 0.81)	0.004
History of cancer	1.57 (1.18-2.10)	0.45 (0.16; 0.74)	0.002	1.41 (1.05-1.88)	0.34 (0.05; 0.63)	0.021
Prior major haemorrhage	2.07 (1.14-3.72)	0.73 (0.14; 1.32)	0.016	2.03 (1.12-3.67)	0.70 (0.11; 0.13)	0.020
Prior stroke/TIA	1.36 (1.03-1.80)	0.31 (0.03; 0.59)	0.028			
Use of PPI	1.35 (1.05-1.74)	0.30 (0.05; 0.55)	0.020			
History of falls	1.93 (1.30-2.90)	0.66 (0.27; 1.05)	0.001			
Creatinine (quartiles)						
2	0.84 (0.58- 1.22)	-0.17 (-0.54; 0.20)	0.367			
3	1.16 (0.80-1.66)	0.15 (-0.22; 0.51)	0.434			
4	1.56 (1.13-2.20)	0.46 (0.12; 0.79)	0.007			
Peripheral arterial disease/PAD	1.49 (0.99-2.24)	0.40 (-0.01; 0.81)	0.053			
Haemoglobin (quartiles)						
2	0.95 (0.66-1.37)	-0.48 (-0.41-0.32)	0.798			
3	0.72 (0.48-1.06)	-0.33 (-0.73-0.59)	0.096			
4	0.67 (0.44-1.04)	-0.39 (-0.82-0.42)	0.077			
Haematocrit	0.98 (0.95-1.01)	-0.02 (-0.52; 0.01)	0.115			
Smoking	0.85 (0.69-1.05)	-0.16 (-0.37; 0.05)	0.131			
Antiplatelet therapy	1.24 (0.91-1.70)	0.22 (-0.10; 0.53)	0.171			
Diabetes	0.80 (0.56-1.11)	-0.24 (-0.58; 0.11)	0.179			
ALAT	0.99 (0.98-1.00)	-0.01 (-0.02; 0.01)	0.284			
Prior gastric ulcer	1.27 (0.77-2.10)	0.24 (-0.27; 0.74)	0.356			
Coronary artery disease	1.16 (0.84-1.60)	0.15 (-0.17; 0.47)	0.362			
Heart Failure	1.12 (0.86-1.47)	0.12 (-0.15; 0.39)	0.402			
Use of NSAID	1.36 (0.62-2.98)	0.31 (-0.47; 1.09)	0.437			
Female sex	0.94 (0.71-1.24)	-0.06 (-0.34; 0.22)	0.678			
History of VTE	1.06 (0.69-1.64)	0.06 (-0.38; 0.50)	0.783			

Thrombocytes	1.00 (0.99-1.00)	0.00 (0.00; 0.00)	0.786
Body-Mass- Index	1.00 (0.98-1.03)	0.00 (-0.02; 0.03)	0.796
Risky alcohol consumption	1.06 (0.58-1.95)	0.06 (-0.55; 0.67)	0.85
Type of Atrial Fibrillation	1.01 (0.89-1.17)	0.02 (-0.13; 0.16)	0.854
Poor INR control	1.01 (0.60-1.70)	0.01 (-0.51; 0.53)	0.969
Treatment with VKA	1.00 (0.79-1.28)	0.00 (-0.24; 0.25)	0.988
Treatment with DOAC	1.00 (0.78-1.27)	0.00 (-0.25; 0.24)	0.988

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1 **Table 3: Predictors included in the score**

	β -coefficient (95% CI)	Points assigned
Age ≥ 75 years	0.476 (0.223 -0.730)	1.5
Hypertension	0.483 (0.157- 0.810)	1.5
History of cancer	0.341 (0.051- 0.631)	1
Prior major bleeding	0.707 (0.112- 1.301)	2
Max Points:		6

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8 **Table 4: Risk category distribution and incidence of bleeding in the derivation and internal**
 9 **validation**

Risk category (Score Points)	Risk category distribution	Incidence of bleeding from derivation		Incidence of bleeding after validation
	n (%)	n per 100 patient years (95% CI)		per 100 patient years (95% CI)
Low (0-1)	394 (18.4)	21	2.5 (1.6-3.8)	2.5 (1.0-4.1)
Moderate (1.5-3)	1579 (73.5)	190	5.9 (5.1- 6.8)	5.9 (4.7-6.9)
High (>3)	174 (8.1)	44	12.9 (9.7-17.4)	12.9 (8.8-17.4)

10 *95% CI =95% Confidence Interval

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Table 5: C-statistics over time our score and existing risk scores applied in our cohort

	No events/no patients	Our Score C-statistics (95% CI)	HAS-BLED	ATRIA	ORBIT	Rutherford Score
Up to 6 months	3/2147	0.79 (0.78 to 0.80)	0.70 (0.45 to 0.94)	0.74 (0.62 to 0.86)	0.59 (0.46 to 0.72)	0.75 (0.43 to 1.06)
Up to 12 months	25/2147	0.71 (0.63 to 0.80)	0.63 (0.52 to 0.74)	0.73 (0.66 to 0.80)	0.69 (0.60 to 0.78)	0.72 (0.63 to 0.82)
Up to 24 months	90/2147	0.66 (0.61 to 0.72)	0.60 (0.54 to 0.65)	0.66 (0.61 to 0.71)	0.64 (0.58 to 0.69)	0.67 (0.61 to 0.72)
Up to 36 months	172/2147	0.64 (0.60 to 0.68)	0.61 (0.56 to 0.65)	0.65 (0.61 to 0.69)	0.63 (0.59 to 0.67)	0.66 (0.61 to 0.70)
Up to 48 months	233/2147	0.64 (0.60 to 0.68)	0.60 (0.56 to 0.64)	0.64 (0.60 to 0.68)	0.62 (0.58 to 0.66)	0.65 (0.61 to 0.69)
Up to 4.4 years	255/2147	0.62 (0.59 to 0.65)	0.60 (0.56 to 0.63)	0.60 (0.57 to 0.64)	0.59 (0.55 to 0.62)	0.62 (0.58 to 0.66)