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R. Pisters, D. A. Lane, R. Nieuwlaat, C. B. de Vos, H. J. G. M. Crijns and G. Y. H. Lip

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Revised

A novel user-friendly score (HAS-BLED) to assess one-year risk of major bleeding in atrial fibrillation patients: The Euro Heart Survey

R Pisters, DA Lane*, R Nieuwlaat, CB de Vos, HJGM Crijns, GYH Lip*

Department of Cardiology,
Maastricht University Medical Centre, The Netherlands

*University of Birmingham Centre for Cardiovascular Sciences,
City Hospital, Birmingham B18 7QH, UK

Corresponding author:
Prof GYH Lip
University of Birmingham Centre for Cardiovascular Sciences,
City Hospital, Birmingham B18 7QH, UK
Tel: +44 121 5075080; Fax: +44 121 554 4083; g.y.h.lip@bham.ac.uk

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Key words: atrial fibrillation; bleeding; oral anticoagulation; bleeding risk score

ABSTRACT

Objective Despite extensive use of oral anticoagulation (OAC) in patients with atrial fibrillation (AF) and the increased bleeding risk associated with such OAC use, no handy quantification tool of assessing this risk exists. We aimed to develop a practical risk score to estimate the one-year risk for major bleeding (intracranial, hospitalization, hemoglobin drop >2g/L and/or transfusion) in a cohort of 'real world' AF patients.

Methods Based on 3978 patients in the EuroHeart Survey on AF with complete follow-up, all univariate bleeding risk factors in this cohort were used in a multivariate analyses along with 'historic' bleeding risk factors. A new bleeding risk score (acronym HAS-BLED: **H**ypertension, **A**bnormal renal/liver function, **S**troke, **B**leeding history or predisposition, **L**abile INR, **E**lderly (>65), **D**rugs/alcohol concomitantly) was calculated, incorporating risk factors from the derivation cohort.

Results Fifty-three (1.5%) major bleeds occurred during 1-year follow-up. The annual bleeding rate rose with increasing risk factors. The predictive accuracy in the overall population using significant risk factors in the derivation cohort (c-statistic 0.72) was consistent when applied in several subgroups. Application of the new bleeding risk score (HAS-BLED) gave similar c-statistics except where patients were receiving antiplatelet agents alone or no antithrombotic therapy, with c-statistics of 0.91 and 0.85, respectively.

Conclusion This simple, novel bleeding risk score (acronym HAS-BLED) provides a practical tool to assess the individual bleeding risk of 'real world' AF patients, potentially supporting clinical decision-making regarding antithrombotic therapy in AF patients.

INTRODUCTION

Atrial fibrillation (AF) is associated with a well-known increase in ischemic stroke risk[1] which is further increased by individual conditions such as heart failure, hypertension, diabetes and prior thromboembolism.[2] Oral anticoagulation (OAC) dramatically reduces this risk[3] and is therefore recommended in AF patients at moderate-high risk of stroke and thromboembolism.[4] The rising incidence and prevalence of AF, increases the likelihood of OAC use in the AF population which is usually elderly, and comorbidities commonly coexist [5,6,7]. Indeed, clinical decision making about whether or not OAC is justified based on stroke risk is supported by various practical stroke risk classification schema which incorporate known clinical risk factors.[4,8]

However, stroke risk is also closely related to bleeding risk,[9] and OAC prescription needs to balance the benefit from stroke prevention against the risk from bleeding. Thus, there is often suboptimal implementation of thromboprophylaxis amongst AF patients[9,10], which may be partly due to the lack of a validated bleeding risk stratification schema that is user-friendly.[11-13] This is further reflected by the absence of recommendations on bleeding risk assessment in current anti-thrombotic guidelines for AF management.[4,12] The available schemas estimating the risk of bleeding associated with use of OAC either do not focus on AF patients in particular[14,15], address a (very) specific subgroup among AF patients[16], or incorporate routinely unavailable risk factors which also overlap significantly with stroke risk factors.[17] Furthermore, all published schema are based on 'historic' cohorts of patients and consequently may not reflect advancements in medical

care over time (for example, OAC monitoring) and treatment of underlying heart disease.[14-17]

Our aim was to develop a practical risk score to estimate the one-year risk of major bleeding (intracranial, hospitalization, haemoglobin drop >2g/L and/or transfusion) in a contemporary, 'real world' cohort of AF patients.

METHODS

We used the large population database of the prospective Euro Heart Survey on AF, with data collected between 2003 and 2004. A detailed study outline of the Euro Heart Survey on AF at baseline[5] and follow-up assessment[18] has been previously described. In summary, 5,333 ambulatory and hospitalized AF patients from 182 university, non-university, and specialized hospitals among 35 member countries of the European Society of Cardiology (ESC) were enrolled. Patients had to be 18 years or older and have an ECG or Holter proven diagnosis of AF during the qualifying admission or in the preceding year. A one year follow-up assessment was performed to determine survival and major adverse cardiovascular events, such as major bleeding. Medical records and/or medical information systems were used to populate the dataset.

We defined *major bleeding* as any bleeding requiring hospitalization and/or causing a decrease in haemoglobin level of more than 2 g/L and or requiring blood transfusion,

which was not a hemorrhagic stroke. *Hemorrhagic stroke* was defined as a focal neurologic deficit of sudden onset, diagnosed by a neurologist, lasting longer than 24 hours and caused by bleeding. Presence of chronic dialysis or renal transplantation or serum creatinine ≥200μmol/L was classified as *abnormal kidney function*. *Abnormal liver function* was defined as chronic hepatic disease (eg. cirrhosis) or biochemical evidence of significant hepatic derangement (eg. bilirubin >2x upper limit of normal, in association with AST/ALT/ALP >3x upper limit normal, etc). Finally, *valvular heart disease* was defined as the presence of any regurgitation or gradient over a valve with hemodynamic significance and/or related symptoms.

Statistical analysis and design of a new bleeding risk score

Data analysis was performed with SPSS (SPSS Inc., Version 16.0). The presence of any differences between the groups with and without a major bleeding during one year follow-up was tested by Fisher's exact test for categorical variables and by independent samples T-test for continuous variables.

All potential bleeding risk factors identified from the univariate analyses of the derivation cohort with a p-value <0.10 (age>65, female gender, diabetes mellitus, heart failure, chronic obstructive pulmonary disease, valvular heart disease (VHD), kidney failure, prior major bleeding episode and clopidogrel use), were used in the multivariate logistic regression analyses along with more 'historical' bleeding risk factors: OAC, alcohol use, and hypertension. We disregarded thyroid disease (p=0.039) because of difficulties with interpretation (only n=10 bleeding events) and this had not been identified as a bleeding

risk in prior systematic reviews[11-13]. Given the persistent nature of the evidence of OAC, hypertension, age>65, renal failure, alcohol abuse and prior major bleed as bleeding risk factors, these variables were kept in the model at all times. The other, less strongly linked, variables were removed stepwise from the model when the *P*-value exceeded 0.10. Variables with $P<0.05$ in the final model were considered to be significant contributors and were checked for interaction effects, which did not exist.

In recognition of the limited number of major bleeds and relatively short follow-up period in the Euro Heart Survey on AF, we also added consistent risk factors for major bleeding(stroke, alcohol use, systolic blood pressure >160mmHg, etc) identified in recent systematic reviews[11,13] to use the data from the derivation cohort to test a new bleeding risk score (HAS-BLED, *see below*) in final statistical model, accepting the lack of statistical significance of some variables in our derivation cohort. For each of the variables in the final model the regression coefficient, net odds ratio (OR) and its 95% confidence interval (CI) and *P*-value are reported (*Table 1*). We then calculated the c-statistic as a measure of the predictive accuracy of the model incorporating bleeding risk factors from the derivation cohort (that is, prior major bleeding, age>65, clopidogrel use and kidney failure), where based on their respective multivariate regression coefficients, two points were awarded for prior major bleeding and one point for each of the other bleeding risk factors. In addition, we report the c-statistics in a subgroup analysis of individuals discharged with OAC monotherapy, OAC combined with an antiplatelet drug, an antiplatelet drug alone, or no antithrombotic therapy.

A new bleeding risk score (acronym **HAS-BLED**: **H**ypertension, **A**bnormal renal/liver function, **S**troke, **B**leeding history or predisposition, **L**abile INR, **E**lderly (>65), **D**rugs/alcohol concomitantly) was calculated, incorporating risk factors from the derivation cohort as well as significant risk factors of major bleeding found in the literature from systematic reviews.[11,13] **HAS-BLED** is an acronym for **H**ypertension [uncontrolled, >160 mmHg systolic), **A**bnormal renal/liver function (1 point for presence of renal or liver impairment, maximum 2 points), **S**troke (previous history, particularly lacunar), **B**leeding history or predisposition [anemia], **L**abile INR [i.e. therapeutic time in range <60%], **E**lderly (>65 years), **D**rugs/alcohol concomitantly (antiplatelet agents, non-steroidal anti-inflammatory drugs; 1 point for drugs plus 1 point for alcohol excess, maximum 2 points) as shown in *Table 2*.

In order to compare the predictive accuracy of our novel bleed risk score (HAS-BLED) with the previously proposed HEMOR$_2$RHAGES scheme, patients were classified accordingly[17]; however, we considered 'uncontrolled' hypertension to be >160 mmHg systolic, a 'history of malignancy' to be similar to 'current malignancy' and we classified ≥8 units alcoholic consumption per week as 'ethanol abuse'. Relevant genetic and laboratory data (required for calculation of the HEMOR$_2$RHAGES schema), apart from serum creatinine, were not available for the Euro Heart Survey on AF cohort.

RESULTS

Of the 5272 AF patients in the Euro Heart Survey of AF who were discharged alive[5], 3456 (66%) patients without mitral valve stenosis or valvular surgery had one year follow-up status regarding major bleeding. The overall mean (SD) age was 66.8 (12.8) years and the majority were male (59%). Fifty-three (1.5%) patients experienced a major bleed during the first year, including 9 (17%) cases of intracerebral hemorrhage (ICH). The baseline demographic and clinical characteristics of the 3456 patients are presented in *Table 3*.

Of all discharged patients, 2242 (64.8%) were on OAC (286 (12.8%) of whom also received aspirin and/or clopidogrel), 828 (24.0%) received antiplatelet therapy alone (aspirin and/or clopidogrel) and 352 (10.2%) received no antithrombotic therapy. The distribution of the risk factors for major bleeding within one year among the different antithrombotic treatment regimens in the derivation cohort is depicted in *Table 4*. The risk of major bleeding within one year in AF patients in the Euro Heart Survey determined by the novel bleeding risk score, HAS-BLED, is shown in *Table 5.* The annual bleeding rate increased with the addition of each risk factor from the derivation cohort *(Table 5)*.

The corresponding unadjusted bleeding rates in patients with OAC, antiplatelet therapy alone, or no antithrombotic treatment were 1.75, 0.97, and 1.42 bleeds per 100 patient years, respectively. The predictive accuracy in the overall population using significant

risk factors in the derivation cohort (c-statistic 0.72) was consistent when applied in several subgroups, as shown in *Table 6*. Application of the new bleeding risk score (HAS-BLED) gave similar c-statistics to that derived in the derivation cohort overall (0.72), or when patients were established on OAC at baseline (0.69) or where patients were on 'OAC plus antiplatelet therapy' at baseline (0,78). HAS-BLED substantially improved the predictive accuracy of bleeding risk where AF patients were receiving antiplatelet therapy alone or in those who were not on antithrombotic therapy at all (with c-statistics of 0.91 and 0.85, respectively). The HEMOR$_2$RHAGES bleeding scheme had a lower predictive accuracy compared to the new HAS-BLED score, overall or in relation to antithrombotic therapy use, except in the 'OAC plus antiplatelet therapy' subgroup [*Table 6*].

Of all the 33 bleeding events in patients discharged with OAC because of a CHADS$_2$ score≥1, 4 (12%) patients had a HAS-BLED-based bleeding risk which outweighed their individual stroke risk. Conversely, of all 1580 patients discharged with OAC because of a CHADS$_2$ score≥1 who did not suffer a major bleed within one year, only 34 (2.2 %) had a HAS-BLED-based bleeding risk that outweighed their individual stroke risk. Of all 21 patients with a CHADS$_2$ score≥1 discharged without OAC who suffered a stroke within one year of follow-up, only one had a HAS-BLED score outweighing the individual stroke risk. Of the CHADS$_2$ score ≥1 patients discharged without OAC with a higher HAS-BLED bleeding risk score, all three patients suffered a major bleed.

DISCUSSION

Using a derivation cohort based on the large, 'real-world' population of the Euro Heart Survey on AF, we identified four independent risk factors of major bleeding within one year (prior major bleeding, age>65, clopidgrel use and kidney failure). Incorporating these risk factors with other established risk factors from systematic reviews and multivariate analyses[11,13,19], we developed and tested a novel, user-friendly bleeding risk score, HAS-BLED, which demonstrated a good predictive accuracy in the overall EuroHeart survey cohort (c-statistic 0.72) but performed particularly well in predicting bleeding risk where antiplatelet therapy was used alone (c-statistic 0.91), or no antithrombotic therapy at all (c-statistic 0.85). Assessment of both stroke and bleeding risk using the $CHADS_2$ and HAS-BLED schemas, respectively, in the Euro Heart Survey on AF population would have resulted in withholding OAC therapy in 12% of the patients who suffered a major bleeding within one year and the initiation of OAC in 95% of the patients at high risk for stroke who were discharged without OAC and had suffered a stroke within one year.

With the previously published $HEMOR_2RHAGES$ schema[17] and others[11,19], the concept of a risk score for major bleeding in AF patients is not new. However, our novel proposed HAS-BLED score has several key advantages over the above-mentioned bleeding risk stratification method. First, the shorter acronym means that physicians have less risk factors to memorize when using the HAS-BLED score, thereby increasing the user-friendliness and subsequent clinical application. Further, in contrast to certain risk factors

incorporated into the HEMOR$_2$RHAGES score which require laboratory parameters or even genetic testing[17], all risk factors of the HAS-BLED score are either readily available from the clinical medical history or routinely tested in (new) AF patients. This characteristic strongly supports its use in all health care settings and is another significant contributor to its superior user-friendliness. Because less does not necessarily mean more, it is important to note that the predictive accuracy of the HAS-BLED score is broadly similar when compared to the HEMOR$_2$RHAGES model in the overall population (c-statistic of 0.72 vs. 0.66, respectively).[17] However, the HAS-BLED score was particularly useful when antiplatelet therapy was used alone or no antithrombotic therapy used at all (c-statistics of 0.91 and 0.85, respectively). Whilst the HAS-BLED score and the HEMOR$_2$RHAGES model were broadly similar in subjects who were not taking antithrombotic therapy at baseline (c-statistics of 0.85 vs 0.81, respectively), the HAS-BLED score is simpler. This score would be particularly useful in everyday clinical practice, when making decisions on whether OAC can be initiated in a newly diagnosed AF patient who is not taking any antithrombotic therapy[12], or where antiplatelet therapy (or NSAIDs) use is being considered, for example, in the setting or coronary artery disease.[20]

As mentioned previously, balancing the individual risk of bleeding and stroke is difficult[21] but of the utmost importance to maximize appropriate antithrombotic therapy and minimise adverse events in AF patients, resulting in a net clinical benefit for the treated patient. In daily clinical practice, the CHADS$_2$ index[8] is a widely used tool to stratify stroke risk in AF patients. For now, the HEMOR$_2$RHAGES score is the only

suitable counterpart available to assess the risk of bleeding.[17] Closer examination of the risk factors comprising the $CHADS_2$ and $HEMOR_2RHAGES$ schemas, reveals an extensive overlap between risk factors for bleeding and stroke, which has obvious drawbacks.[8,17] Indeed, the patients at highest stroke and thromboembolic risk are – paradoxically - more likely to sustain bleeding complications. This may lead to confusion when trying to decide on the most appropriate antithrombotic regimen, to balance the risks of bleeding against the risk of stroke, thereby limiting the applicability of such schemas.

The 'trade off' in terms of the benefits and risks of OAC using the $CHADS_2$ index and HAS-BLED score demonstrates that in the vast majority of AF patients who require OAC ($CHADS_2$ index ≥ 2) the risk of bleeding outweighs the potential benefit of OAC if the HAS-BLED bleed score exceeds the individual $CHADS_2$ index. In case of a $CHADS_2$ score of 1 the HAS-BLED score must exceed two for the potential harm caused by OAC use to offset its beneficial effect on stroke risk reduction. Appropriate use of this practical 'rule' in the Euro Heart Survey on AF population could have prevented more than one out of every ten (4/33) of the major bleeds. However, 34/1580 (2.2%) of the patients with a $CHADS_2$ score≥ 1 discharged with OAC who did not suffer a major bleed within one year would have been denied OAC because of a HAS-BLED bleed risk outweighing their stroke risk.

The potential impact on current clinical practice of the novel HAS-BLED score is underlined by the recently published Atrial Fibrillation Clopidogrel Trial with Irbesartan

for Prevention of Vascular Events (ACTIVE)-A trial.[22] This large randomized clinical trial was designed to compare the preventive effect on all cause vascular events of clopidogrel plus aspirin vs. aspirin alone in AF patients deemed unsuitable for OAC treatment. In half (n~3,500) of these AF patients with a high stroke risk, the most common applied classification was 'unsuitable for OAC', which was solely based on physician clinical judgement, without the presence of any predefined risk factor of bleeding or other objective risk scoring. Perhaps this reflects physician's uncertainty about what to consider as true risk factors of bleeding and their fear of potential iatrogenic harm caused by OAC use.

Given the recent promising results of the RE-LY trial[23], patients assessed as being at higher bleeding risk using the novel HAS-BLED score could be prescribed the lower dose (110mg bid) of the oral direct thrombin inhibitor, Dabigatran, which demonstrated a significant reduction in major bleeding compared to warfarin, with a similar stroke risk reduction to warfarin, whilst those at lower bleeding risk could be prescribed Dabigatran 150mg bid which offers superior efficacy but with a similar major bleeding risk to warfarin[24]. Further, the HAS-BLED score could also be used to identify patients who may benefit from a left atrial appendage occlusion device[25], i.e. patients at high risk of ischemic stroke who have such an increased risk of bleeding that OAC is contraindicated. Thus, future clinical decisions by physicians deciding on initiating OAC (whether with the VKAs or new oral anticoagulants, such as dabigatran) in an AF patient could use the HAS-BLED score to assess the potential bleeding risk and feel more confident in prescribing OAC where appropriate or refer for implantation of a left atrial appendage

occlusion device. Indeed, bleeding risk scores should also be validated in dabigatran-treated patients, as well as those being considered for left atrial appendage occlusion devices.

Limitations

The HAS-BLED score need to be validated in at least one other large contemporary cohort of AF patients before it can be widely implemented into daily practice. Potential selection bias might have occurred because of 25% missing data regarding the occurrence of major bleeding during the follow-up period. Patients who were lost to follow-up were likely to have been more comorbidities and transferred to nursing homes or even deceased, which might have led to underestimation of the overall bleeding rate. Also, we recognize that the limited number of major bleeds and the relatively short follow-up period make it possible that other important risk factors for bleeding were not identified. Indeed, bleeding may occur following changes to warfarin (eg. for surgery or interventions such as pacemaker implant, etc.) with institution of 'bridging' therapy with low molecular heparin. We also did not consider thyroid disease in our model, as this had not been identified as a bleeding risk in prior systematic reviews[11-13]; however, some pathophysiological plausibility is possible, since hypothyroidism has been described to cause acquired von Willebrand disease associated with low Factor VIII levels and platelet dysfunction[26]. Of note, there is an improved predictive power of the HAS-BLED score over the HEMOR$_2$RHAGES score in patients treated with antiplatelet therapy(or NSAIDs) or no antithrombotic therapy at all (*Table 6*).

The risk of major bleeding (especially intracranial hemorrhage) is increased with advanced age[26,7,28]. Of note, the risk of major haemorrhage can be similar amongst elderly patients receiving warfarin and aspirin[29]. The relatively small numbers of bleeding events and the modest size of the very elderly in our cohort makes it rather difficult to draw too many firm conclusions by introducing different weights to different age categories (eg. 1 point for age 65-74, 2 points for age 75-84, 3 points for age≥85, etc), as well as introducing additional complexity to our simple HAS-BLED scoring system. Also, age is a continuous (rather than categorized) risk for bleeding (as well as stroke). It must be stressed that in many instances, bleeding risk amongst the elderly is multifactorial[30] and is often the result of associated comorbidities, high anticoagulation intensity and labile INRs in this population[11-13]. The HAS-BLED score already takes some of these aspects into account, allowing cumulative assessment of risk factors for bleeding. In the present analysis, the HAS-BLED score already outperforms the $HEMOR_2RHAGES$ bleeding scheme, which was an attempt by Gage et al[17] to have a 'simple' method of bleeding assessment. Future validation and refinement of HAS-BLED amongst a huge elderly AF population with prolonged follow-up may address the issue of age as a continuous variable for bleeding risk.

Finally, data about INR control are obviously not available when having to decide on starting OAC for the first time in a patient. When on OAC, the INR is often elevated at the time of admission for a bleeding event, but it is unknown which measure of INR control best predicts bleeding in such a manner that clinical action could prevent the bleeding. We did not include actual INR values during follow-up, but acknowledge its

importance as risk factor of bleeding.[19] Of note, the current alternative ($HEMOR_2RHAGES$ model) was also developed without the availability of INR values.[17]

Conclusion

We propose a novel bleeding risk score, HAS-BLED, which provides an easy, practical tool to assess the individual bleeding risk of AF patients, potentially supporting clinical decision-making regarding antithrombotic therapy for stroke prevention.

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Conflicts of interest

None declared.

Authors contributions

RP, RN – statistical analyses, data interpretation, drafting of manuscript

DL, CV, HC – drafting, revision of manuscript

GYHL – study design and hypothesis, concept of the HAS-BLED score (the 'Birmingham Atrial Fibrillation Bleeding schema'), data interpretation, drafting of manuscript, revisions

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Table 1. Clinical risk factors for major bleeding within one year in atrial fibrillation patients enrolled in the Euro Heart Survey

	Multivariate regression coefficient	Event rate with risk factor	Event rate without risk factor	Univariate p-value	Odds ratio (95% CI)	MV p-value
Systolic BP>160	-0.52	4 (1.0)	11 (1.4)	0.515	0.60 (0.21-1.72)	0.337
Kidney failure	1.05	10 (5.4)	43 (1.3)	<0.001	2.86 (1.33-6.18)	0.007
Stroke	-0.44	4 (2.1)	48 (1.5)	0.532	0.94 (0.32-2.86)	0.940
Prior major bleeding	2.02	9 (14.8)	44 (1.3)	<0.001	7.51 (3.00-18.78)	<0.001
Age >65	0.98	42(2.3)	11 (0.7)	<0.001	2.66 (1.33-5.32)	0.007
Anti-platelet agent□	-0.22	5 (3.4)	46 (1.4)	0.066	0.81 (0.43-1.51)	0.504
Alcohol use*	-16.80	10 (1.6)	31 (1.9)	1.000	0.00 (0.00-)	0.996

BP, Blood Pressure, CI, confidence interval; *>8 units per week; □aspirin or clopidogrel

Table 2. Clinical characteristics comprising the HAS-BLED bleeding risk score

Letter	Clinical characteristic*	Points awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (age >65)	1
D	Drugs or alcohol (1 point each)	1 or 2
		Maximum 9 points

* 'Hypertension' is defined as systolic blood pressure >160 mmHg. 'Abnormal kidney function' is defined as the presence of chronic dialysis or renal transplantation or serum creatinine ≥200μmol/L. 'Abnormal liver function' is defined as chronic hepatic disease (eg. cirrhosis) or biochemical evidence of significant hepatic derangement (eg. bilirubin >2x upper limit of normal, in association with AST/ALT/ALP >3x upper limit normal, etc). 'Bleeding' refers to previous bleeding history and/or predisposition to bleeding eg. bleeding diathesis, anaemia, etc. 'Labile INRs' refers to unstable/high INRs or poor time in therapeutic range (eg. <60%). Drugs/alcohol use refers to concomitant use of drugs, such as antiplatelet agents, non-steroidal anti-inflammatory drugs, etc.

Table 3. Baseline characteristics of atrial fibrillation patients from the Euro Heart Survey with a known follow-up status regarding major bleeding

Characteristic, n (%)	**Bleed (n=53)**	**No bleed (n=3910)**	**p value**
Mean (SD) age, years	73 (10)	66 (13)	<0.001
Age >65	42 (79)	1748 (51)	<0.001
Female sex	28 (53)	1329 (39)	0.046
Mean (SD) Body Mass Index, kg/m^2	27 (5)	28 (8)	0.298
Atrial Fibrillation type, n (%)			0.827
First detected	9 (17)	628 (19)	
Paroxysmal	15 (28)	1029 (31)	
Persistent/permanent	29 (56)	1688 (51)	
Medical History, n (%)			
Current smoker	6(11)	450 (13)	0.716
Hypertension	39 (74)	2228 (65)	0.245
Diabetes Mellitus	12 (23)	610 (18)	0.367
Coronary artery disease	15 (29)	1182 (35)	0.462
Heart failure	24 (45)	994 (24)	0.014
Valvular heart disease†	18 (34)	607 (18)	0.006
Chronic obstructive pulmonary disease	12 (23)	427 (13)	0.037
Thyroid disease	10 (20)	326 (10)	0.059
Stroke/transient ischaemic attack	6 (12)	355 (11)	0.818
Mean (SD) $CHADS_2$ score*	2.07 (1.16)	1.60 (1.27)	0.008
Bleeding risk factors, n (%)			
Prior major bleed	9 (17)	52 (2)	<0.001
Mean (SD) systolic blood pressure	137(20)	136 (22)	0.856
Malignancy	4 (8)	183 (5)	0.529
Renal failure	10 (19)	174 (5)	<0.001
Alcohol use ≥8 units/week	0 (0)	170 (5)	0.111

*$CHADS_2$, congestive heart failure, hypertension, age>75, diabetes mellitus and previous stroke / transient ischemic attack (doubled)

Table 4. Clinical risk factors of major bleeding within one year in atrial fibrillation patients of the Euro Heart Survey according to antithrombotic treatment at discharge

Bleeding risk factor	Oral anticoagulation (n=2115)	Aspirin/clopidogrel (n=828)	Neither (n=352)
Systolic BP>160 (%)	10.0	13.4	13.7
Kidney failure (%)	5.3	4.8	6.8
Stroke (%)	5.9	5.0	3.2
Prior major bleeding (%)	1.7	1.6	3.2
Age >65 (%)	53.3	52.8	42.6
Antiplatelet agent (%)	12.1	100	0.0
Alcohol use* (%)	5.7	4.8	5.0

* ≥8units/week

Table 5. The risk of major bleeding within one year in atrial fibrillation patients enrolled in the Euro Heart Survey

	Derivation cohort*			HAS-BLED**		
Risk factors/score	**n**	**no. of bleeds**	**Bleeds per 100 patient-years**	**n**	**no. of bleeds**	**Bleeds per 100 patient-years**
0	1517	9	0.59	798	9	1.13
1	1589	24	1.51	1286	13	1.02
2	219	7	3.20	744	14	1.88
3	41	8	19.51	187	7	3.74
4	14	3	21.43	46	4	8.70
5	1	0	-	8	1	12.50
6	....	....	....	2	0	0.0
7	...	...	...	0	...	...
8	...	...	...	0	...	...
9	...	...	...	0	...	...
Any score	3381	51	1.51	3071	48	1.56
P value for trend			<0,001			0.007

*Derivation cohort risk factors in multivariate analysis: Bleeding history [given 2 points], Age>65 years, Clopidogrel use and Kidney failure [Maximum score 5]

**HAS-BLED, acronym: Hypertension [uncontrolled, >160 mmHg systolic), Abnormal renal/liver function, Stroke, Bleeding history or predisposition [anemia], Labile INR [i.e. therapeutic time in range <60%], Elderly (>65) and Drugs/alcohol concomitantly [antiplatelet agents, non-steroidal anti-inflammatory drugs] [Maximum score 9].

Table 6. Predictive power of the bleeding risk scores used to assess risk of major bleeding within one year in atrial fibrillation patients

Antithrombotic treatment	Bleeding risk score	N	C-statistic (CI)
Overall group	Derivation cohort*	3381	0.72 (0.64-0.79)
	HAS-BLED**	3071	0.72 (0.65-0.79)
	HEMOR$_2$RHAGES†	3040	0.66 (0.57-0.74)
Oral anticoagulation alone	Derivation cohort*	1947	0.68 (0.58-0.78)
	HAS-BLED**	1722	0.69 (0.59-0.80)
	HEMOR$_2$RHAGES	1706	0.64 (0.53-0.75)
OAC + antiplatelet therapy	Derivation cohort*	240	0.80 (0.68-0.93)
	HAS-BLED**	239	0.78 (0.65-0.91)
	HEMOR$_2$RHAGES	235	0.83 (0.74-0.91)
Antiplatelet therapy alone	Derivation cohort*	788	0.74 (0.52-0.97)
	HAS-BLED**	753	0.91 (0.83-1.00)
	HEMOR$_2$RHAGES	728	0.83 (0.68-0.98)
No antithrombotic therapy	Derivation cohort*	348	0.75 (0.51-0.99)
	HAS-BLED	315	0.85 (0.00-1.00)
	HEMOR$_2$RHAGES	311	0.81 (0.00-1.00)

N, number of patients included in analysis; CI, confidence interval; OAC, oral anticoagulation).

*Derivation cohort risk factors: Bleeding history, Age>65 years, Clopidogrel use and Kidney failure

**HAS-BLED, acronym: Hypertension [uncontrolled, >160 mmHg systolic), Abnormal renal/liver function, Stroke, Bleeding history or predisposition [anemia], Labile INR [i.e. therapeutic time in range <60%], Elderly (>65 years) and Drugs/alcohol concomitantly [antiplatelet agents, non-steroidal anti-inflammatory drugs;

†HEMOR$_2$RHAGES, acronym: Hepatic or renal disease, Ethanol abuse, Malignancy, Older age (>75years), Re-bleeding, Reduced platelet count or function, Hypertension (uncontrolled), Anemia, Genetic factors, Excessive fall risk and Stroke.

[NB. Classifying bleeding risk by antithrombotic therapy use with the HEMOR$_2$RHAGES model resulted in mean scores of 1.17, 1.17, 1.31, 1.24 and 1.07, respectively.]

A novel user-friendly score (HAS-BLED) to assess one-year risk of major bleeding in atrial fibrillation patients: The Euro Heart Survey

R. Pisters, D. A. Lane, R. Nieuwlaat, C. B. de Vos, H. J. G. M. Crijns and G. Y. H. Lip

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