Assessing the Risk of Bleeding in Patients With Atrial Fibrillation

The Loire Valley Atrial Fibrillation Project

Gregory Y. H. Lip, MD*; Amitava Banerjee, MPH, DPhil; Isabelle Lagrenade, MD; Deirdre A. Lane, PhD; Sophie Taillandier, MD; Laurent Fauchier, MD, PhD*

Background—Management decisions for thromboprophylaxis in atrial fibrillation need to balance the risk of stroke against serious hemorrhage. The objective of the present analysis is to compare the Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (>65 years), Drugs/alcohol concomitantly (HAS-BLED) score against other older bleeding risk scores and the new Anticoagulation and Risk Factors in Atrial Fibrillation score in an atrial fibrillation cohort.

Methods and Results—Patients diagnosed with nonvalvular atrial fibrillation in a 4-hospital institution between 2000 and 2010 were identified. Independent risk factors of bleeding were investigated using Cox regression. The predictive value of several bleeding risk schema was assessed using the c-statistic and net reclassification improvement. Oral anticoagulation use was highest in moderate-risk patients (59.8%) but only slightly more than high-risk (50.1%) and low-risk (46.4%) patients. Those at higher bleeding risk (HAS-BLED ≥3) were also at highest risk of stroke/thromboembolism or stroke/thromboembolism/death, as well as bleeding and all-cause mortality. On multivariable analysis, independent predictors of bleeding were age ≥75 years and age ≥65 years, alcohol excess, anemia, and heart failure. All risk scores had only modest predictive ability for bleeding, whether on vitamin K antagonist or not (c-statistic ≈0.6). When the HAS-BLED score was compared with other bleeding risk scores, the net reclassification improvement was significantly improved against all other scores tested.

Conclusions—Current oral anticoagulation prescribing patterns would suggest that bleeding risk estimation by clinicians is poor and that oral anticoagulation prescribing does not reflect bleeding risk per se. The HAS-BLED score performs well in relation to predicting bleeding events compared with older bleeding scores and the Anticoagulation and Risk Factors in Atrial Fibrillation score, with significantly improved reclassification using HAS-BLED compared with all other bleeding risk scores tested. (***Circ Arrhythm Electrophysiol*. 2012;5:941-948.**)

Key Words: bleeding risk ■ atrial fibrillation ■ anticoagulation

Atrial fibrillation (AF) confers an increased risk of stroke and thromboembolism (TE), which is associated with high mortality and morbidity. The use of oral anticoagulation (OAC) therapy results in a 64% reduction in stroke and a 26% reduction in all-cause mortality compared with control/placebo.[1] Nonetheless, OAC confers a significant risk of serious bleeding, at least in historical trials,[1] although more contemporary data suggest no significant difference between OAC and aspirin.[2–4]

Clinical Perspective on p 948

Management decisions need to be individualized when considering thromboprophylaxis, balancing the risk of stroke against the risk of serious hemorrhage. This has led to the analysis of net clinical benefit comparing ischemic stroke with intracranial hamorrhage, at least for vitamin K antagonist (VKA; eg, warfarin) therapy.[5,6] Thus, more attention has been directed toward the assessment of bleeding risk. Indeed, the availability of new oral anticoagulants, such as dabigatran, has focused more attention on bleeding risk assessment, given that in some countries 2 doses are available, with the lower dose (110 mg BID) recommended for those at high bleeding risk.[7]

Although risk factors for bleeding are well recognized, many of these risk factors are also risk factors for stroke.[8] In the 2006 United Kingdom National Institute for Health and Clinical Excellence guidelines, bleeding risk factors associated with OAC therapy were mentioned, but no formal bleeding scoring system was recommended[9] because the available bleeding risk scores were complicated, with only one derived

Received April 3, 2012; accepted July 18, 2012

From the University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, United Kingdom (G.Y.H.L., A.B., D.A.L.); and Service de Cardiologie, Pôle Coeur Thorax Vasculaire, Centre Hospitalier, Universitaire Trousseau et Faculté de Médecine, Université François Rabelais (I.L., S.T., L.F.), Tours, France.

*These authors contributed equally as senior authors to this work.

The online-only Data Supplement is available at http://circep.ahajournals.org/lookup/suppl/doi:10.1161/CIRCEP.112.972869/-/DC1.

Correspondence to Gregory Y. H. Lip, MD, University of Birmingham, Centre for Cardiovascular Sciences, City Hospital, Birmingham B18 7QH, United Kingdom. E-mail g.y.h.lip@bham.ac.uk

Circ Arrhythm Electrophysiol **is available at http://circep.ahajournals.org** **DOI: 10.1161/CIRCEP.112.972869**

and validated in an AF cohort.[10] In the 2006 American College of Cardiology/American Heart Association/European Society of Cardiology guidelines,[11] bleeding risk assessment was not even considered. In 2010, the European Society of Cardiology guidelines recommended bleeding risk assessment, advocating the use of new Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (>65 years), Drugs/alcohol concomitantly (HAS-BLED) score, which has the advantage of simplicity of calculation and where a score ≥3 necessitates caution and regular review.[12,13] The 2011 Canadian Cardiovascular Society guidelines and their subsequent 2012 focused update also recommended bleeding risk assessment and use of HAS-BLED score.[14,15]

The HAS-BLED score was first proposed in 2010 after its derivation and validation in the EuroHeart survey.[13] Since then, this score has been validated in various independent real-world cohorts[16–18] and 1 trial cohort.[19] The HAS-BLED score has only been compared with the older schemes in 2 cohorts, one being the EuroHeart survey[13] and the other, a clinical trial cohort[19]; no formal comparisons with the new Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) bleeding score[20] have been undertaken in an AF cohort representative of routine real-world clinical practice. The ATRIA score is a weighted score derived from a selected prospective cohort of anticoagulated AF patients, although various limitations have been highlighted.[21]

The objective of the present analysis is to compare the HAS-BLED score against other older bleeding risk scores and the newer ATRIA score in a representative AF cohort. We tested the hypothesis that the HAS-BLED score would perform well as other older and relatively more complicated bleeding risk scores, as well as the new ATRIA score, in routine clinical practice.

Methods

Study Population

At the Centre Hospitalier Régional et Universitaire in Tours (France), all patients diagnosed with nonvalvular AF or atrial flutter by the Department of Cardiology between 2000 and 2010 were identified. The institution includes a total of 4 hospitals covering all medical and surgical specialties, the only public institution in an area of around 4000 km², serving ≈400 000 inhabitants. Patients with nonvalvular AF evaluated by the cardiology department were defined as those directly admitted to the inpatient cardiology service and those seen as a consultation in any service and subsequently proposed for admission in the cardiology department. The diagnosis of AF as confirmed by a cardiologist was needed to avoid the wrong diagnosis and to ensure that other diagnoses related to cardiac conditions were reliable because these were important factors used for calculating the several scores used.

Patients were followed from the first record of nonvalvular AF after January 1, 2000 (ie, index date), up to the latest data collection at the time of study (December 2010). Treatment at discharge was obtained by screening hospitalization reports, and information on comorbidities was obtained from the computerized coding system.

During follow-up, information on the study outcomes of major bleeding was recorded. Major bleeding was defined as bleeding with a reduction in the hemoglobin level of at least 20 g/L, or with transfusion of at least 1 unit of blood, or symptomatic bleeding in a critical area or organ (eg, intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome), or bleeding that causes death. All information on bleeding was identified with the diagnosis coded in a subsequent hospitalization during follow-up; thus, we recorded all hospitalizations with a bleed as an additional criterion for major bleeding.

Bleeding Risk

For each patient, the HAS-BLED score was calculated as the sum of points obtained after adding 1 point for the presence of each individual factor.[22] Patients with an HAS-BLED score of 0 were deemed to have low bleeding risk, 1 to 2 as intermediate/moderate risk, and ≥3 as high bleeding risk.

We then tested the predictive value of several bleeding risk schema in this cohort: $HEMORR_2HAGES$ Risk Factors (score),[23] Beyth et al,[24] Kuijer et al,[25] Shireman et al,[22] and ATRIA[20] (online-only Data Supplement Table I). For each risk stratification schema, we calculated the c-statistic as a measure of predictive accuracy. In the $HEMORR_2HAGES$ scheme, we considered systolic blood pressure >160 mm Hg as uncontrolled hypertension, a history of malignancy as similar to current malignancy, 20 units of alcohol consumption weekly as ethanol abuse, creatine clearance <50 mL/min as renal disease, and a low platelet count less than the lower limit of normal and hemoglobin content less than the lower limit of normal as anemia. Relevant genetic and laboratory data (required for calculation of some schemes), apart from serum creatinine and hematocrit, were not available. For HAS-BLED, labile international normalized ratio was defined as <60% time in the therapeutic range (international normalized ratio 2–3 inclusive), concomitant platelet inhibitor agents as aspirin or nonsteroidal anti-inflammatory drugs, and elderly as age >65 years.

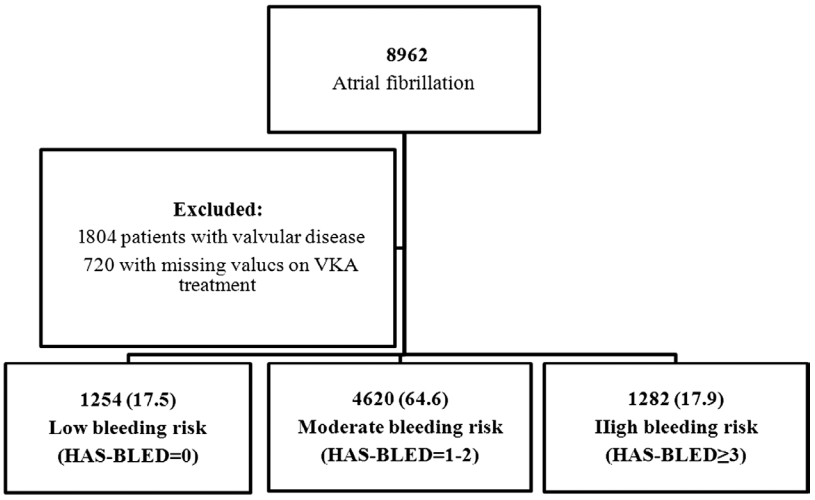

Figure. Study population. Figure shows patient population studied in relation to inclusion/exclusion and categories of Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly (HAS-BLED) score. VKA indicates vitamin K antagonist.

Table 1. Characteristics of Patients With Atrial Fibrillation by Bleeding Risk as Assessed by the HAS-BLED Scoring System

n (%)	High Bleeding Risk (HAS-BLED ≥3) n=1254	Moderate Bleeding Risk (HAS-BLED=1–2) n=4620	Low Bleeding Risk (HAS-BLED=0) n=1282	*P* Value	Age-Adjusted *P* Value
Mean age (SD)	77.7 (8.2)	73.8 (11.6)	49.0 (13.1)	<0.001	…
Female	488 (38.9)	1823 (39.5)	393 (30.7)	<0.001	<0.001
Type of AF					
Paroxysmal	725 (57.8)	2543 (55.0)	908 (70.8)		
Permanent	476 (38.0)	1815 (39.3)	313 (24.4)	<0.001	0.03
Persistent	53 (4.2)	262 (5.7)	61 (4.8)		
Comorbidities					
Hypertension	1073 (85.6)	1959 (42.4)	0 (0.0)	<0.001	<0.001
Diabetes mellitus	337 (26.9)	706 (15.3)	65 (5.1)	<0.001	<0.001
Previous stroke	339 (27.0)	248 (5.4)	7 (0.5)	<0.001	<0.001
Coronary artery disease	774 (61.7)	1270 (27.5)	86 (6.7)	<0.001	<0.001
Any vascular disease	856 (68.3)	1404 (30.4)	100 (7.8)	<0.001	<0.001
Heart failure	817 (65.2)	2484 (53.8)	329 (25.7)	<0.001	<0.001
Renal impairment	390 (31.1)	162 (3.5)	0 (0.0)	<0.001	<0.001
Liver impairment	15 (1.2)	4 (0.1)	0 (0.0)	<0.001	<0.001
Dyslipidemia	427 (34.1)	821 (17.8)	115 (9.0)	<0.001	<0.001
Smoking	252 (20.1)	548 (11.9)	117 (9.1)	<0.001	<0.001
Pacemaker/ICD	221 (17.6)	802 (17.4)	131 (10.2)	<0.001	0.41
Bleeding risk factors					
Previous bleeding	230 (18.3)	99 (2.1)	0 (0.0)	<0.001	<0.001
Labile INR	80 (6.4)	42 (0.9)	0 (0.0)	<0.001	<0.001
Anemia	16 (1.3)	20 (0.4)	5 (0.4)	0.001	0.03
NSAIDs	6 (0.5)	4 (0.1)	0 (0.0)	0.001	0.006
Drugs	686 (54.7)	549 (11.9)	0 (0.0)	<0.001	<0.001
Cancer (active)	35 (2.8)	78 (1.7)	6 (0.5)	<0.001	0.01
Excessive risk of falls	24 (1.9)	51 (1.1)	1 (0.1)	<0.001	0.40
Thrombocytopenia	2 (0.2)	4 (0.1)	0 (0.0)	0.38	0.51
Antithrombotic agents					
Vitamin K antagonist	593 (50.1)	2455 (59.8)	559 (46.4)	<0.001	0.002
Antiplatelets	788 (67.2)	1208 (30.2)	279 (23.5)	<0.001	<0.001
Any antithrombotic	1074 (91.6)	3251 (81.4)	808 (68.0)	<0.001	<0.001
Other medical therapy					
ACE-I	335 (47.2)	862 (39.0)	108 (22.8)	<0.001	<0.001
β-blocker	390 (54.9)	1007 (45.6)	221 (46.7)	<0.001	<0.001
Digoxin	170 (23.9)	649 (29.4)	149 (31.5)	0.006	<0.001
Diuretic	395 (55.6)	957 (43.3)	101 (21.4)	<0.001	<0.001
Antiarrhythmic agent	390 (51.0)	1293 (50.1)	243 (40.4)	<0.001	0.09
Calcium channel blocker	65 (25.1)	203 (19.4)	25 (9.1)	<0.001	0.11
$CHADS_2$					
Mean (SD)	2.96 (1.21)	1.73 (1.05)	0.32 (0.53)	<0.001	<0.001
Low (score=0)	8 (0.6)	566 (12.3)	912 (71.1)	<0.001	<0.001
Intermediate (score=1)	115 (9.2)	1394 (30.2)	333 (26.0)	<0.001	<0.001
High (score ≥2)	1131 (90.2)	2660 (57.5)	37 (2.9)	<0.001	<0.001
CHA_2DS_2-VASc					
Mean (SD)	4.99 (1.36)	3.24 (1.34)	0.70 (0.72)	<0.001	<0.001
Low (score=0)	0 (0.0)	38 (0.8)	567 (44.2)	<0.001	<0.001

(continued)

Table 1. (Continued)

n (%)	High Bleeding Risk (HAS-BLED ≥3) n=1254	Moderate Bleeding Risk (HAS-BLED=1–2) n=4620	Low Bleeding Risk (HAS-BLED=0) n=1282	*P* Value	Age-Adjusted *P* Value
Intermediate (score=1)	1 (0.1)	406 (8.8)	545 (42.5)	<0.001	<0.001
High (score ≥2)	1253 (99.9)	4176 (90.4)	170 (13.3)	<0.001	<0.001

AF indicates atrial fibrillation; ICD, implantable cardiac defibrillator; INR, international normalized ratio; $CHADS_2$, 1 point each for congestive heart failure, hypertension, age ≥75, and diabetes mellitus, and 2 points for previous stroke or thromboembolism; CHA_2DS_2-VASc, 1 point for congestive heart failure, hypertension, diabetes mellitus, vascular disease, age 65 to 74, and female sex, and 2 points for previous stroke or thromboembolism and age ≥75; HAS-BLED, hypertension, abnormal renal and liver function, stroke, bleeding history or predisposition, labile international normalized ratio (INR), elderly (>65 y); NSAIDs, nonsteroidal anti-inflammatory drugs; ACE, angiotensin-converting enzyme.

Statistical Analysis

The study population was stratified into 3 categories according to HAS-BLED scores of bleeding risk, that is, high risk (HAS-BLED ≥3), moderate risk (HAS-BLED=1–2), and low risk (HAS-BLED=0) (Figure). Baseline characteristics were determined separately for the 3 bleeding risk strata, and differences were investigated using χ^2 test for categorical covariates and Kruskal-Wallis test for continuous covariates (Table 1). In each of the 3 bleeding risk categories, event rates of stroke/TE, bleeding, and death were calculated for patients with AF who were not receiving VKA.

The bleeding risk associated with the individual risk factors of the HAS-BLED score was estimated in Cox proportional hazard models. To increase the power of the analyses, the Cox regression models included patients with and without VKA; this approach was appropriate because no interaction was found between the effect of the individual risk factors and VKA treatment. Also, the recent analysis by Friberg et al[17] clearly shows that the major bleeding (and intracranial hemorrhage) rates on VKA were similar to aspirin-treated (ie, nonanticoagulated) patients, even when subdivided by HAS-BLED scores. Of note, the 2010 European guidelines state that the HAS-BLED score should be used "… to assess bleeding risk … (with) the initiation of antithrombotic therapy, whether with oral anticoagulation or aspirin."[12]

Both univariable (including the individual risk factor and VKA treatment only) and multivariable (including all the HAS-BLED risk factors and VKA) Cox regression models were applied. Furthermore, the event rates of bleeding were calculated in patients with and without each of the HAS-BLED risk factors.

The hazard ratios associated with each of the 6 bleeding risk scores HAS-BLED,[13] $HEMORR_2HAGES$,[23] Beyth et al,[24] Kuijer et al,[25] Shireman et al,[22] and ATRIA[20] were calculated by Cox regression (for the scores as continuous and categorical variables). For each risk scoring system, the c-statistic was calculated and compared with the HAS-BLED c-statistic using the DeLong test. The categorical version of the net reclassification improvement (NRI) was used to compare the reclassification by HAS-BLED versus other risk scoring systems.

A 2-sided $P<0.05$ was considered statistically significant for all analyses. All analyses were performed with SPSS statistical software version 18.0 (IBM).

Results

Our cohort consisted of 7156 patients with AF, of which 1254 (17.5%) were at high bleeding risk (HAS-BLED score ≥3), 4620 (64.6%) were at moderate risk (HAS-BLED 1–2), and 1282 (17.9%) were at low risk (HAS-BLED=0) (Figure). Patient demography and clinical features are summarized in Table 1. Paroxysmal AF was more common among low-risk subjects, whereas various clinical risk factors (eg, hypertension), prior bleeding, and an excessive risk of falls were, unsurprisingly, more common among high-risk subjects. VKA use was highest in moderate-risk patients (59.8%) but only slightly more than that in high-risk (50.1%) and low-risk (46.4%) patients. High-risk patients also had high stroke risk, as reflected by their $CHADS_2$ (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, previous Stroke[doubled]) or CHA_2DS_2-VASc (Congestive heart failure, Hypertension, Age ≥75 years, diabetes mellitus, previous Stroke, Vascular disease, Age 65–74 years, Sex category [female]) scores.

Event rates for stroke, TE, death, and bleeding are shown in Table 2. Those at high bleeding risk (HAS-BLED ≥3) were also at highest risk of the composite end point of stroke/TE or stroke/TE/death, as well as bleeding and all-cause mortality.

On multivariable analysis, independent predictors of bleeding were age ≥75 (hazard ratio, 1.42 [95% CI, 1.14–1.76]) and age ≥65 (1.43 [1.11–1.86]) years, alcohol excess (2.27 [1.14–4.53]), anemia (2.49 [1.27–4.88]), heart failure (1.23 [1.01–1.50]), and VKA therapy (1.28 [1.01–1.62]) (Table 3). Excessive risk of falls, concomitant drugs, smoking, and hypertension had point estimates suggestive of risk, but 95% CIs were wide and included 1.0. Major bleeding

Table 2. Event Rates (95% CIs) per 100 Person-Years in Patients With Atrial Fibrillation

	High Bleeding Risk (HAS-BLED ≥3) n=1254		Moderate Bleeding Risk (HAS-BLED=1–2) n=4620		Low Bleeding Risk (HAS-BLED=0) n=1282		
	Events	Event Rate	Events	Event Rate	Events	Event Rate	*P**
Stroke	131	1.04 (0.87–1.24)	301	0.65 (0.58–0.73)	23	0.18 (0.11–0.27)	<0.001
Stroke/TE	155	1.24 (1.05–1.45)	362	0.78 (0.7–0.87)	28	0.22 (0.15–0.32)	<0.001
Stroke/TE/death	339	2.70 (2.42–3.01)	795	1.72 (1.6–1.84)	63	0.49 (0.38–0.63)	<0.001
Major bleeding	158	1.26 (1.07–1.47)	343	0.74 (0.67–0.83)	49	0.38 (0.28–0.51)	<0.001
All-cause death	249	1.99 (1.75–2.25)	558	1.21 (1.11–1.31)	40	0.31 (0.22–0.42)	<0.001

TE indicates thromboembolism; HAS-BLED, hypertension, abnormal renal and liver function, stroke, bleeding history or predisposition, labile international normalized ratio (INR), elderly (>65 y).

*P value for 2-sided χ^2 test.

Table 3. Hazard Ratio (95% CI) of Major Bleeding in Patients With Atrial Fibrillation

	Univariable	Multivariable
	HR (95% CI)	HR (95% CI)
Hypertension	1.39 (1.18–1.64)	1.11 (0.91–1.35)
Renal impairment	2.34 (1.86–2.95)	*
Liver impairment	0.65 (0.09–4.65)	*
Liver/renal impairment	2.30 (1.83–2.89)	*
Previous stroke	1.50 (1.16–1.94)	1.27 (0.96–1.69)
Previous bleeding	1.56 (1.12–2.17)	1.22 (0.84–1.76)
Labile INR	1.36 (0.84–2.21)	1.14 (0.69–1.88)
Age ≥75 y	1.66 (1.40–1.97)	1.42 (1.14–1.76)
Age ≥65 y	1.73 (1.40–2.14)	1.43 (1.11–1.86)
Drugs	1.38 (1.12–1.69)	1.44 (0.66–3.13)
Alcohol	1.63 (1.15–2.29)	2.27 (1.14–4.53)
Drugs/alcohol	1.42 (1.17–1.72)	0.75 (0.33–1.66)
Diabetes mellitus	1.33 (1.08–1.65)	1.13 (0.89–1.43)
Anemia	2.79 (1.49–5.21)	2.49 (1.27–4.88)
Excessive risk of falls	1.74 (0.86–3.50)	1.53 (0.75–3.10)
Cancer	1.41 (0.82–2.45)	1.00 (0.55–1.83)
Smoking	1.24 (1.00–1.54)	1.13 (0.88–1.44)
Heart failure	1.47 (1.24–1.74)	1.23 (1.01–1.50)
Male sex	1.15 (0.97–1.37)	0.82 (0.67–1.00)
Antithrombotic therapy	1.39 (1.06–1.82)	1.16 (0.88–1.53)
VKA use	1.25 (1.04–1.50)	1.28 (1.01–1.62)

HR indicates hazard ratio; INR, international normalized ratio; VKA, vitamin K antagonist.

*CIs too wide to calculate HR.

Table 4. Major Bleeding Rates (95% CI) per 100 Person-Years in Patients With Atrial Fibrillation and Not Receiving Vitamin K Antagonist

	With Risk Factor	Without Risk Factor
Hypertension	0.75 (0.60–0.93)	0.52 (0.42–0.64)
Renal impairment	1.10 (0.72–1.61)	0.57 (0.48–0.66)
Liver impairment	0.77 (0.02–4.29)	0.61 (0.52–0.71)
Liver/renal impairment	1.10 (0.72–1.60)	0.56 (0.48–0.66)
Previous stroke	0.74 (0.42–1.22)	0.60 (0.51–0.70)
Previous bleeding	1.10 (0.63–1.79)	0.58 (0.50–0.68)
Labile INR*	0.40 (0.01–2.23)	0.61 (0.52–0.71)
Age ≥75 y	0.71 (0.58–0.87)	0.52 (0.41–0.65)
Age ≥65 y	0.71 (0.60–0.84)	0.41 (0.29–0.56)
Drugs†	0.80 (0.60–1.03)	0.55 (0.45–0.66)
Alcohol	0.77 (0.31–1.58)	0.60 (0.52–0.70)
Drugs/alcohol	0.79 (0.61–1.02)	0.54 (0.44–0.65)
Diabetes mellitus	0.66 (0.43–0.96)	0.60 (0.51–0.71)
Anaemia	1.58 (0.33–4.61)	0.60 (0.52–0.70)
Excessive risk of falls	0.75 (0.21–1.93)	0.61 (0.52–0.70)
Cancer	0.75 (0.21–1.93)	0.61 (0.52–0.70)
Smoking	0.74 (0.49–1.07)	0.59 (0.50–0.69)
Heart failure	0.77 (0.63–0.94)	0.48 (0.38–0.60)
Male sex	0.67 (0.55–0.81)	0.53 (0.41–0.67)

INR indicates international normalized ratio; VKA, vitamin K antagonist; NSAID, nonsteroidal anti-inflammatory drug.

*As this table refers to patients not receiving VKA treatment, some patients may have had a history of labile INR (while previously receiving VKA) and were not treated with VKA at discharge of their hospitalization in the cardiology department.

†The D was quoted when patients, in addition to their anticoagulant treatment for AF, were also treated with any other concomitant medication with a risk of bleeding (aspirin, NSAID, etc).

rates in patients with AF and not receiving VKA are shown in Table 4 in relation to the presence or absence of risk factors. All risk scoring systems tested (whether as categorical or continuous score, as relevant) resulted in a significant hazard ratio for increased bleeding on univariable analysis (Table 5).

The predictive value for bleeding events, evidenced by c-statistics for the various scores, is presented in Table 6. All scores had only modest predictive ability for bleeding whether on VKA or not (c-statistic ≈0.60), with the HAS-BLED score having a c-statistic (and 95% CIs) better than chance, whether tested as a continuous or categorical (ie, low, moderate, and high risk) score, in both VKA-treated and non-VKA–treated patients.

For patients on VKA, the $HEMORR_2HAGES$, Kuijer, and Shireman scores were not significantly better than chance (95% CIs for c-statistics include 0.50) when tested as a categorical variable. For patients on non-VKA, the $HEMORR_2HAGES$, Kuijer, Shireman, and ATRIA scores were not significantly better than chance (95% CIs for c-statistics include 0.50) when tested as a categorical variable (ie, low, moderate, and high risk).

When the HAS-BLED score was compared with other bleeding risk scores, the NRI was significantly improved against all other scores tested (Table 7). The HAS-BLED scoring system led to a (significant) positive NRI compared with the other 5 commonly used bleeding risk scoring systems (ranging from 6.6% with ATRIA to 11.7% with Shireman).

Discussion

In this study, we have shown how the HAS-BLED score performs in relation to predicting bleeding events compared with older bleeding scores ($HEMORR_2HAGES$,[23] Beyth et al,[24] Kuijer et al,[25] Shireman et al[22]) and the new ATRIA score.[20] Although the predictive ability using the c-statistic was modest (≈0.6) for most of the scores, the NRI showed improved reclassification using HAS-BLED compared with all other tested bleeding risk scores, including ATRIA. Of the tested scores, only the HAS-BLED score had a c-statistic (and 95% CIs) better than chance, whether tested as a continuous or categorical (ie, low, moderate, and high risk) score, in both VKA-treated and non-VKA–treated patients

Unsurprisingly, patients with paroxysmal AF were more common among subjects at low risk of bleeding, but while VKA use was highest in moderate-risk patients this was only slightly higher than those patients who were at high or low risk using the HAS-BLED score. Given that some of the decisions about VKA use were made before the availability of the HAS-BLED score[13] and publication of the 2010 European Society of Cardiology guidelines,[12] this would suggest that bleeding risk estimation by clinicians was poor, and OAC prescribing practice did not reflect bleeding risk per se.

Table 5. Comparison of Hazard Ratio (95% CI) of Major Bleeding in Patients With Atrial Fibrillation by Different Scoring Systems

	Overall	Moderate Risk*		High Risk*	
	Univariable HR (95% CI); *P*	Univariable HR (95% CI); *P*	Proportion (%)†	Univariable HR (95% CI); *P*	Proportion (%)†
As continuous variable					
HAS-BLED*	1.40 (1.31–1.51); *P*<0.001	…	…	…	…
$HEMORR_2HAGES$*	1.48 (1.35–1.61); *P*<0.001	…	…	…	…
Beyth*	1.61 (1.45–1.78); *P*<0.001	…	…	…	…
Kuijer*	1.14 (1.05–1.23); *P*<0.001	…	…	…	…
Shireman*	2.13 (1.76–2.58); *P*<0.001	…	…	…	…
ATRIA†	1.26 (1.20–1.31); *P*<0.001	…	…	…	…
As categorical variable					
HAS-BLED	1.85 (1.60–2.13); *P*<0.001	2.00 (1.48–2.70); *P*<0.001	64.6	3.57 (2.59–4.92); *P*<0.001	17.9
$HEMORR_2HAGES$	1.80 (1.49–2.17); *P*<0.001	1.85 (1.48–2.31); *P*<0.001	10.8	2.90 (1.50–5.61); *P*=0.002	0.8
Beyth	2.04 (1.70–2.45); *P*<0.001	2.11 (1.68–2.66); *P*<0.001	70.8	3.97 (2.62–6.03); *P*<0.001	2.6
Kuijer	1.66 (1.32–2.08); *P*<0.001	1.77 (1.35–2.30); *P*<0.001	82.4	2.30 (1.24–4.27); *P*=0.01	1.6
Shireman	1.75 (1.42–2.16); *P*<0.001	1.73 (1.38–2.15); *P*<0.001	13.4	3.94 (1.27–12.26); *P*=0.02	0.1
ATRIA	1.61 (1.41–1.84); *P*<0.001	2.09 (1.46–3.00); *P*<0.001	2.7	2.48 (1.88–3.27); *P*<0.001	5.3

HR indicates hazard ratio; HAS-BLED, hypertension, abnormal renal and liver function, stroke, bleeding history or predisposition, labile international normalized ratio (INR), elderly (>65 y).

*Hazard ratio compared with low-risk category (assumed to be HR 1.0).

†Proportion of total patients in risk category (%).

High-risk patients also had high stroke risk, as reflected by $CHADS_2$ or CHA_2DS_2-VASc scores. Indeed, this translated to the observation that those at high bleeding risk (HAS-BLED ≥3) were also at highest risk of stroke/TE or stroke/TE/death, as well as bleeding and all-cause mortality. Gallego et al[18] recently reported that the HAS-BLED score was a good predictor of major bleeding (c-statistic ≈0.7), being as good as a multivariable analysis; however, the HAS-BLED score was only modestly predictive of cardiovascular events or death and less good compared with multivariable analysis for these outcomes because it is a score designed to predict bleeding rather than cardiovascular events or death. Other independent analyses comparing the HAS-BLED score have also found its predictive value to be as good as, and possibly better, than the older scores,[16,17] with the highest c-statistic (≈0.8) in anticoagulated subjects seen in the nationwide cohort study by Olesen et al.[16] However, it would be inappropriate to directly compare c-statistics in one study with another, given the differences in study population, follow-up, and so on.

Table 6. Comparison of c-Statistics (95% CIs) for Different Bleeding Risk Scoring Systems in Patients With Atrial Fibrillation

	C-statistic (95% CI)†		
	All Patients	Patients on VKA	Patients Not on VKA
HAS-BLED‡	0.61 (0.59–0.63)	0.61 (0.58–0.65)	0.60 (0.56–0.64)
HAS-BLED§	0.59 (0.57–0.61)	0.58 (0.55–0.61)	0.60 (0.54–0.64)
HEMORR2HAGES‡	0.58 (0.56–0.61)	0.59 (0.56–0.62)	0.59 (0.54–0.63)
HEMORR2HAGES§	0.54 (0.51–0.56)	0.53 (0.50–0.57)	0.55 (0.50–0.59)
Beyth‡	0.60 (0.57–0.62)	0.60 (0.56–0.63)	0.60 (0.56–0.64)
Beyth§	0.57 (0.54–0.59)	0.56 (0.53–0.59)	0.58 (0.54–0.62)
Kuijer‡	0.52 (0.50–0.55)*	0.52 (0.49–0.55)*	0.54 (0.50–0.58)
Kuijer§	0.53 (0.50–0.55)*	0.53 (0.50–0.56)	0.53 (0.49–0.57)
Shireman‡	0.56 (0.54–0.58)	0.56 (0.53–0.60)	0.57 (0.53–0.61)
Shireman§	0.52 (0.50–0.55)*	0.53 (0.50–0.56)	0.53 (0.48–0.57)
ATRIA‡	0.59 (0.57–0.62)	0.60 (0.56–0.63)	0.59 (0.55–0.64)
ATRIA§	0.54 (0.52–0.57)	0.55 (0.52–0.59)	0.47 (0.42–0.51)

HAS-BLED indicates hypertension, abnormal renal and liver function, stroke, bleeding history or predisposition, labile international normalized ratio (INR), elderly (>65 y).

†c-statistic calculated as area under the curve for the receiver-operator characteristic (ROC).

‡As a continuous variable.

§As a categorical variable (low, moderate, or high risk).

*P<0.05 in 2-tailed DeLong test compared with HAS-BLED score.

Table 7. Comparison of the NRI Between HAS-BLED and Other Contemporary Bleeding Risk Schemas

	Difference in Predicted Probability of an Event					
HAS-BLED vs	Patients With Event	Patients Without event	NRI	SE	z Score	*P* Value
$HEMORR_2HAGES$	0.271	−0.159	0.112	0.023	4.87	<0.0001
Beyth	0.233	−0.142	0.091	0.021	4.26	<0.0001
Kuijer	0.265	−0.151	0.115	0.024	4.81	<0.0001
Shireman	0.282	−0.165	0.117	0.023	5.01	<0.0001
ATRIA	0.184	−0.117	0.066	0.021	3.18	0.0007

HAS-BLED score indicates hypertension, abnormal renal and liver function, stroke, bleeding history or predisposition, labile international normalized ratio (INR), elderly, drugs/alcohol concomitantly score; NRI: net reclassification improvement.

In this cohort, independent predictors of bleeding were age (whether categorized as age ≥75 years or age ≥65 years), alcohol excess, and anemia (reflective perhaps of bleeding tendency or predisposition), which are represented within the HAS-BLED score. Other elements of HAS-BLED, such as concomitant drugs and hypertension, were not statistically significant, although point estimates were suggestive of increased risk. Interestingly, heart failure, excessive risk of falls, and smoking were also suggestive of risk. In an analysis of bleeding risk factors from the Stroke Prevention using an Oral Direct Thrombin Inhibitor in Atrial Fibrillation trials, heart failure (as reflected by left ventricular systolic dysfunction) also emerged as an independent risk factor for bleeding.[19] The impact of heart failure on bleeding risk scoring systems merits further consideration in further analyses.

All risk scoring systems tested (whether as categorical or continuous score, as relevant) resulted in a significant hazard for increased bleeding on univariable analyses. However, the predictive value for bleeding events, as evident by c-statistics, only showed modest predictive ability for bleeding whether on VKA or not (c-statistic ≈0.6). Major limitations of the c-statistic for assessing the predictive value have been highlighted, and other methods, such as the NRI, have been proposed.[26,27] In the present study, when the HAS-BLED score was compared with other bleeding risk scores, the NRI was significantly improved (by 6.6%–11.7%) against all other scores tested, including the new ATRIA score.

Study Limitations

The limitations of this registry have been previously reported, with the inherent limitations of diagnostic coding and case ascertainment, particularly if an enrolled patient moved away from the area or had an outcome event in another area. Nevertheless, most patients with a major or fatal bleed, as far as it is identified, are likely to be seen in one department of our institution and not in any other institution. Our definition of major bleeding is also slightly different from the International Society of Thrombosis and Hemostasis definition, because we included the criterion of transfusion of at least 1 unit of blood, instead of 2 units used within the International Society of Thrombosis and Hemostasis definition; although this was partly because blood transfusion was coded in our hospital records (rather than units of blood), our criteria would be more inclusive of bleeding complications, where evident.

Despite statistical adjustment for several risk factors, the nonrandomized cohort design does not exclude the possibility of residual confounding factors. The present study was to focus on testing the hypothesis that the HAS-BLED score would perform well as other older and relatively more complicated bleeding risk scores in clinical practice (in this case, hospital practice). There may be clinical differences between inpatients and outpatients, which would affect the generalizability of our findings to the outpatient setting or to AF diagnosed outside the cardiology department. Inpatients usually have an acute illness or decompensation of a chronic illness that leads to hospitalization, which is different from outpatients. For example, heart failure, which impacts bleeding risk in our study, may be underrepresented in an outpatient or primary care cohort. Patients with AF seen in the cardiology department were 53% of all AF patients seen in the institution and 82% of all AF patients seen in several medical departments of our institution. Our study population is, therefore, representative of inpatients presenting to hospital with AF but may not wholly reflect the AF population in the outpatient or primary care setting.

Conclusions

In relation to predicting bleeding events, the HAS-BLED score outperforms older bleeding scores and the new ATRIA score. Indeed, the NRI showed improved reclassification using HAS-BLED compared with all other tested bleeding risk scores. Of note, OAC prescribing patterns would suggest that bleeding risk estimation by clinicians was poor and OAC prescribing practice did not reflect bleeding risk per se. Therefore, formal assessment of bleeding risk with (preferably) the HAS-BLED score would enhance clinical decision making, as recommended in current guidelines.[12,14,15]

Acknowledgments

Drs Fauchier, Lagrenade, and Taillandier made the primary contribution to data collection. Drs Banerjee, Lip, Lane, and Fauchier contributed to the study conception and design. Dr Banerjee performed the analyses. All authors contributed to interpretation of results, revising the article critically for important intellectual content, and all approved the final article.

Disclosures

Dr Lane has received funding for research and educational symposia from Bayer Healthcare and Boehringer Ingelheim and is a member of the ACCP9 Writing Committee. Prof Lip has served as a consultant for Bayer, Astellas, Merck, AstraZeneca, Sanofi Aventis, Biotronik, BMS/Pfizer, and Boehringer Ingelheim and has been on the speakers bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, and Sanofi Aventis. Dr Fauchier has served as a consultant for Bayer, Medtronic, and Sanofi Aventis and has received funding for conference travel and educational symposia from Boehringer Ingelheim, Bayer, Medtronic, and Sanofi Aventis. The other authors have no conflicts to report.

References

1. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med*. 2007;146:857–867.
2. Connolly SJ, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S, Flaker G, Avezum A, Hohnloser SH, Diaz R, Talajic M, Zhu J, Pais P, Budaj A, Parkhomenko A, Jansky P, Commerford P, Tan RS, Sim KH, Lewis BS,

Van Mieghem W, Lip GY, Kim JH, Lanas-Zanetti F, Gonzalez-Hermosillo A, Dans AL, Munawar M, O'Donnell M, Lawrence J, Lewis G, Afzal R, Yusuf S; AVERROES Steering Committee and Investigators. Apixaban in patients with atrial fibrillation. *N Engl J Med*. 2011;364:806–817.
3. Mant J, Hobbs FD, Fletcher K, Roalfe A, Fitzmaurice D, Lip GY, Murray E; BAFTA investigators; Midland Research Practices Network (MidReC). Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. *Lancet*. 2007;370:493–503.
4. Lip GY, Andreotti F, Fauchier L, Huber K, Hylek E, Knight E, Lane D, Levi M, Marín F, Palareti G, Kirchhof P; European Heart Rhythm Association. Bleeding risk assessment and management in atrial fibrillation patients. Executive Summary of a Position Document from the European Heart Rhythm Association [EHRA], endorsed by the European Society of Cardiology [ESC] Working Group on Thrombosis. *Thromb Haemost*. 2011;106:997–1011.
5. Singer DE, Chang Y, Fang MC, Borowsky LH, Pomernacki NK, Udaltsova N, Go AS. The net clinical benefit of warfarin anticoagulation in atrial fibrillation. *Ann Intern Med*. 2009;151:297–305.
6. Olesen JB, Lip GY, Lindhardsen J, Lane DA, Ahlehoff O, Hansen ML, Raunsø J, Tolstrup JS, Hansen PR, Gislason GH, Torp-Pedersen C. Risks of thromboembolism and bleeding with thromboprophylaxis in patients with atrial fibrillation: A net clinical benefit analysis using a 'real world' nationwide cohort study. *Thromb Haemost*. 2011;106:739–749.
7. Pengo V, Crippa L, Falanga A, Finazzi G, Marongiu F, Palareti G, Poli D, Testa S, Tiraferri E, Tosetto A, Tripodi A, Manotti C; Italian Federation of Thrombosis Centers. Questions and answers on the use of dabigatran and perspectives on the use of other new oral anticoagulants in patients with atrial fibrillation. A consensus document of the Italian Federation of Thrombosis Centers (FCSA). *Thromb Haemost*. 2011;106:868–876.
8. Kirchhof P, Lip GY, Van Gelder IC, Bax J, Hylek E, Kääb S, Schotten U, Wegscheider K, Boriani G, Ezekowitz M, Diener H, Heidbuchel H, Lane D, Mont L, Willems S, Dorian P, Vardas P, Breithardt G, Camm AJ. Comprehensive risk reduction in patients with atrial fibrillation: Emerging diagnostic and therapeutic options. Executive summary of the report from the 3rd AF-NET/EHRA consensus conference. *Thromb Haemost*. 2011;106:1012–1019.
9. Hughes M, Lip GY; Guideline Development Group for the NICE national clinical guideline for management of atrial fibrillation in primary and secondary care. Risk factors for anticoagulation-related bleeding complications in patients with atrial fibrillation: a systematic review. *QJM*. 2007;100:599–607.
10. Tay KH, Lane DA, Lip GY. Bleeding risks with combination of oral anticoagulation plus antiplatelet therapy: is clopidogrel any safer than aspirin when combined with warfarin? *Thromb Haemost*. 2008;100:955–957.
11. Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Le Heuzey JY, Kay GN, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann S, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Halperin JL, Hunt SA, Nishimura R, Ornato JP, Page RL, Riegel B, Priori SG, Blanc JJ, Budaj A, Camm AJ, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo JL, Zamorano JL; American College of Cardiology/American Heart Association Task Force on Practice Guidelines; European Society of Cardiology Committee for Practice Guidelines; European Heart Rhythm Association; Heart Rhythm Society. ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation*. 2006;114:e257–e354.
12. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenek B, Heldal M, Hohloser SH, Kolh P, Le Heuzey JY, Ponikowski P, Rutten FH. Guidelines for the management of atrial fibrillation: the task force for the management of atrial fibrillation of the European Society of Cardiology (ESC). *Eur Heart J*. 2010;31:2369–2429.
13. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest*. 2010;138:1093–1100.
14. Cairns JA, Connolly S, McMurtry S, Stephenson M, Talajic M; CCS Atrial Fibrillation Guidelines Committee. Canadian Cardiovascular Society atrial fibrillation guidelines 2010: prevention of stroke and systemic thromboembolism in atrial fibrillation and flutter. *Can J Cardiol*. 2011;27:74–90.
15. Skanes AC, Healey JS, Cairns JA, Dorian P, Gillis AM, McMurtry MS, Mitchell LB, Verma A, Nattel S; Canadian Cardiovascular Society Atrial Fibrillation Guidelines Committee. Focused 2012 update of the Canadian Cardiovascular Society atrial fibrillation guidelines: recommendations for stroke prevention and rate/rhythm control. *Can J Cardiol*. 2012;28:125–136.
16. Olesen JB, Lip GY, Hansen PR, Lindhardsen J, Ahlehoff O, Andersson C, Weeke P, Hansen ML, Gislason GH, Torp-Pedersen C. Bleeding risk in 'real world' patients with atrial fibrillation: comparison of two established bleeding prediction schemes in a nationwide cohort. *J Thromb Haemost*. 2011;9:1460–1467.
17. Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. *Eur Heart J*. 2012;33:1500–1510.
18. Gallego P, Roldán V, Torregrosa JM, Gálvez J, Valdés M, Vicente V, Marín F, Lip GY. Relation of the HAS-BLED bleeding risk score to major bleeding, cardiovascular events, and mortality in anticoagulated patients with atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2012;5:312–318.
19. Lip GY, Frison L, Halperin JL, Lane DA. Comparative validation of a novel risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation: the HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) score. *J Am Coll Cardiol*. 2011;57:173–180.
20. Fang MC, Go AS, Chang Y, Borowsky LH, Pomernacki NK, Udaltsova N, Singer DE. A new risk scheme to predict warfarin-associated hemorrhage: The ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) Study. *J Am Coll Cardiol*. 2011;58:395–401.
21. Olesen JB, Pisters R, Roldans V, Marin F, Lane DA. The ATRIA risk scheme to predict warfarin-associated hemorrhage not ready for clinical use. *J Am Coll Cardiol*. 2012;59:194–195.
22. Shireman TI, Howard PA, Kresowik TF, Ellerbeck EF. Combined anticoagulant-antiplatelet use and major bleeding events in elderly atrial fibrillation patients. *Stroke*. 2004;35:2362–2367.
23. Gage BF, Yan Y, Milligan PE, Waterman AD, Culverhouse R, Rich MW, Radford MJ. Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF). *Am Heart J*. 2006;151:713–719.
24. Beyth RJ, Quinn LM, Landefeld CS. Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with warfarin. *Am J Med*. 1998;105:91–99.
25. Kuijer PM, Hutten BA, Prins MH, Büller HR. Prediction of the risk of bleeding during anticoagulant treatment for venous thromboembolism. *Arch Intern Med*. 1999;159:457–460.
26. Cook NR. Use and misuse of the receiver operating characteristic curve in risk prediction. *Circulation*. 2007;115:928–935.
27. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med*. 2008;27:157–172.

CLINICAL PERSPECTIVE

Management decisions for thromboprophylaxis in atrial fibrillation need to balance the risk of stroke against serious hemorrhage. In this study, we assessed anticoagulation use in relation to calculated bleeding risk and compared the HAS-BLED score against other older bleeding risk scores ($HEMORR_2HAGES$) and the new ATRIA score in an atrial fibrillation cohort. On multivariable analysis, independent predictors of bleeding were age ≥75 years and age ≥65 years, alcohol excess, anemia, and heart failure. We found that current oral anticoagulation prescribing patterns would suggest that bleeding risk estimation by clinicians is poor and that oral anticoagulation prescribing does not reflect bleeding risk per se. The HAS-BLED score performed well in relation to predicting bleeding events compared with other older bleeding scores and the new ATRIA score, with significantly improved reclassification using HAS-BLED compared with all other bleeding risk scores tested.