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

Gregory Y. H. Lip, MD,* Lars Frison, PHD,† Jonathan L. Halperin, MD,‡ Deirdre A. Lane, PHD*

Birmingham, England; Mölndal, Sweden; and New York, New York

Objectives   The purpose of this study was to investigate predictors of bleeding in a cohort of anticoagulated patients and to evaluate the predictive value of several bleeding risk stratification schemas.

Background   The risk of bleeding during antithrombotic therapy in patients with atrial fibrillation (AF) is not homogeneous, and several clinical risk factors have been incorporated into clinical bleeding risk stratification schemas. Current risk stratification schemas for bleeding during anticoagulation therapy have been based on complex scoring systems that are difficult to apply in clinical practice, and few have been derived and validated in AF cohorts.

Methods   We investigated predictors of bleeding in a cohort of 7,329 patients with AF participating in the SPORTIF (Stroke Prevention Using an ORal Thrombin Inhibitor in Atrial Fibrillation) III and V clinical trials and evaluated the predictive value of several risk stratification schemas by multivariate analysis. Patients were anticoagulated orally with either adjusted-dose warfarin (target international normalized ratio 2 to 3) or fixed-dose ximelagatran 36 mg twice daily. Major bleeding was centrally adjudicated, and concurrent aspirin therapy was allowed in patients with clinical atherosclerosis.

Results   By multivariate analyses, significant predictors of bleeding were concurrent aspirin use (hazard ratio [HR]: 2.10; 95% confidence interval [CI]: 1.59 to 2.77; $p < 0.001$); renal impairment (HR: 1.98; 95% CI: 1.42 to 2.76; $p < 0.001$); age 75 years or older (HR: 1.63; 95% CI: 1.23 to 2.17; $p = 0.0008$); diabetes (HR: 1.47; 95% CI: 1.10 to 1.97; $p = 0.009$), and heart failure or left ventricular dysfunction (HR: 1.32; 95% CI: 1.01 to 1.73; $p = 0.041$). Of the tested schemas, the new HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) score performed best, with a stepwise increase in rates of major bleeding with increasing HAS-BLED score ($p_{trend} < 0.0001$). The c statistic for bleeding varied between 0.50 and 0.67 in the overall entire cohort and 0.68 among patients naive to warfarin at baseline (n = 769).

Conclusions   This analysis identifies diabetes and heart failure or left ventricular dysfunction as potential risk factors for bleeding in AF beyond those previously recognized. Of the contemporary bleeding risk stratification schemas, the new HAS-BLED scheme offers useful predictive capacity for bleeding over previously published schemas and may be simpler to apply.   (J Am Coll Cardiol 2011;57:173–80) © 2011 by the American College of Cardiology Foundation

Atrial fibrillation (AF) is associated with a substantial risk of stroke and systemic embolism. Thromboprophylaxis with oral anticoagulation (OAC) is most effective in reducing stroke compared with antiplatelet therapy (1,2). Compared with

**Abbreviations
and Acronyms**

AF = atrial fibrillation

CI = confidence interval

HR = hazard ratio

INR = international
normalized ratio

LV = left ventricular

OAC = oral anticoagulation

OAC, antiplatelet therapy confers a smaller benefit for stroke prevention (1,2) and is associated with similar rates of major bleeding, particularly among elderly patients with AF (3).

Given that increasing numbers of patients with AF will be treated with OAC, attention has been directed toward estimation of both stroke and bleeding risk to guide the selection of the most appropriate prophylactic measures. Accurate estimation of stroke and bleeding risks is difficult (4), leading to the development of various stroke risk stratification schemas to help identify subjects who may benefit most from OAC therapy because of their higher intrinsic risk of stroke (5). Like the thromboembolic risk of patients with AF, the risk of bleeding during anticoagulation is not homogeneous, and various clinical risk factors have been identified that are associated with incremental bleeding risk. Current schemes for bleeding risk stratification by Shireman et al. (6), Gage et al. (7) (with the acronym HEMORR$_2$HAGES), Beyth et al. (8), and Kuijer et al. (9) have been difficult to apply in clinical practice. Some use complex scoring systems (6,9), and only a few have been derived (and validated) in patients with AF (7,10), with others derived from general anticoagulated populations that may have different clinical profiles from those of AF patients (who are often older with more comorbidities and polypharmacy) (8).

Thus, contemporary guidelines simply list risk factors for bleeding and given the lack of a simple, pragmatic, widely accepted method for bleeding risk assessment applicable to patients with AF, no specific schema is currently recommended for routine clinical use (11). It is recognized that several risk factors predisposing to bleeding are also risk factors for stroke (12), and although some schemas (e.g., CHADS$_2$ [congestive heart failure, hypertension, age >75 years, diabetes mellitus and previous stroke or transient ischemic attack (doubled)] [13]) have modest value for predicting stroke, they are very good at predicting a patient's risk of bleeding (14,15).

We recently derived and validated the HAS-BLED bleeding risk schema for AF (also called the Birmingham AF bleeding schema: Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) in a European cohort (16). The predictive accuracy of this schema was good in the overall population, especially when patients were treated with antiplatelet agents alone or with no antithrombotic therapy, but further validation and comparison with other published bleeding risk schemas are necessary.

The objective of this analysis was to determine risk factors for bleeding and compare the performance of bleeding risk stratification schemas in a large cohort of anticoagulated AF patients in a contemporary clinical trial. To achieve this, we used the combined dataset of the SPORTIF (Stroke Prevention Using an ORal Thrombin Inhibitor in Atrial Fibrillation) III and V trials, which compared warfarin with the oral direct thrombin inhibitor ximelagatran for the prevention of stroke and systemic embolism in patients with AF at moderate to high risk of stroke (17,18). Although ximelagatran was not inferior to well-controlled warfarin in reducing the risk of stroke and systemic embolism in these trials (17,18), concerns about liver safety led to the withdrawal of ximelagatran from further clinical development.

Patients and Methods

The SPORTIF III and V clinical trials were designed as noninferiority phase III trials comparing ximelagatran with warfarin in patients with nonvalvular AF at moderate to high risk of thromboembolism, and a pooled analysis of the results of both trials was pre-specified. SPORTIF III was an open-label trial in 23 countries (17), whereas SPORTIF V was a double-blind trial conducted in North America (18). Inclusion criteria for both trials were similar and included age 18 years and older, persistent or paroxysmal AF, and at least 1 of the following stroke risk factors: hypertension (defined as high blood pressure requiring antihypertensive medication, but below 180/100 mm Hg at randomization), age 75 years and older, previous stroke, transient ischemic attack or systemic embolic event; left ventricular (LV) dysfunction (ejection fraction <40% or symptomatic heart failure), age 65 years and older with coronary artery disease, and age 65 years and older with diabetes mellitus. End points were evaluated in a blinded manner by a central events adjudication committee.

We initially investigated predictors of bleeding risk in the combined SPORTIF III and V trial cohort of 7,329 subjects. Major bleeding was defined as fatal or clinically overt bleeding associated with either transfusion of ≥2 U of blood or ≥20 g/l decrease in hemoglobin or bleeding involving a critical anatomic site other than the brain parenchyma. Intracerebral bleeding counted as primary efficacy events. Clinically overt bleeding not satisfying criteria for major bleeding was classified as minor bleeding.

We then tested the predictive value of several bleeding risk schemas in this cohort: Shireman et al. (6), HEMORR$_2$HAGES (7), Beyth et al. (8), Kuijer et al. (9), and HAS-BLED (16) (Table 1). For each risk stratification schema, we calculated the c statistic as a measure of predictive accuracy. In the HEMORR$_2$HAGES scheme, we considered blood pressure >160 mm Hg systolic as uncontrolled hypertension, a history of malignancy as similar to current malignancy, alcohol consumption of 20 U weekly as ethanol abuse creatinine clearance <50 ml/min as renal disease, a low platelet count as less than the lower limit

Table 1	**Contemporary Bleeding Risk Stratification Schemas**			
	Low	Moderate	High	**Calculation of Bleeding Risk Score**
Kuijer et al., 1999 (9)	0	1–3	>3	(1.6 × age) + (1.3 × sex) + (2.2 × cancer) with 1 point for age ≥60 yrs, female or malignancy, and 0 if none
Beyth et al., 1998 (8)	0	1–2	≥3	Age ≥65 yrs, GI bleed in past 2 weeks, previous stroke, comorbidities (recent MI, Hct <30%, diabetes, creatinine >1.5 ml/l) with 1 point for presence of each condition and 0 if absent
Gage et al., 2006 (7)	0–1	2–3	≥4	HEMORR$_2$HAGES score: liver/renal disease, ETOH abuse, malignancy, age >75 yrs, low platelet count or function, rebleeding risk, uncontrolled hypertension, anemia, genetic factors (CYP2C9), risk of fall or stroke, with 1 point for each risk factor present with 2 points for previous bleed
Shireman et al., 2006 (6)	≤1.07	>1.07–<2.19	>2.19	(0.49 × age >70 yrs) + (0.32 × female) + (0.58 × remote bleed) + (0.62 × recent bleed) + (0.71 × alcohol/drug abuse) + (0.27 × diabetes) + (0.86 × anemia) + (0.32 × antiplatelet drug use) with 1 point for presence of each, and 0 if absent
Pisters et al., 2010 (16)	0	1–2	≥3	HAS-BLED score: Hypertension, Abnormal Renal/Liver Function (1 point each), Stroke, Bleeding History or Predisposition, Labile INR, Elderly Drugs/Alcohol concomitantly (1 point each); maximum 9 points

ETOH = ethyl alcohol; GI = gastrointestinal; Hct = hematocrit; INR = international normalized ratio; MI = myocardial infarction.

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 the SPORTIF AF cohort. For HAS-BLED, labile INR was defined as <60% time in the therapeutic range (INR 2 to 3 inclusive), concomitant platelet inhibitor agents as aspirin or nonsteroidal anti-inflammatory drugs (clopidogrel was not allowed in the trial), elderly older than 75 years of age, given that the majority of patients (76%) in the cohort were older than 65 years of age. In addition, we report the c statistics in subgroups of individuals who were warfarin naive at baseline as well as those taking warfarin plus aspirin concurrently.

Statistical analysis. Categorical data were evaluated with the Fisher exact test or the chi-square test for >2 categories and continuous data using Student *t* test. All tests were performed 2-tailed, with p values ≤0.05 considered statistically significant. No adjustment was made for multiple testing because all reported results are explorative. Annualized event rates assume constant rates over time. Unless otherwise stated, all analyses were performed on pooled data from the SPORTIF III and V trial cohorts. All randomized patients were included in the intention-to-treat population. An on-treatment analysis accounted for time until therapy was interrupted for up to 30 consecutive days (or up to 60 days for cardioversion) or 60 days cumulatively. Assessment of major bleeding used the on-treatment approach. Given the wide range of time in the studies for individual patients (common study closure, intended duration of study treatment ranging between 12 and 26 months), statistical analyses had to take time at risk into account; this was done either through Cox regression analyses or by using patient-years as analyses unit. All analyses on major bleeding in this paper are based on on-treatment analyses (17,18). Patients are contributing with time at risk as long as they are receiving study treatment (according to the on-treatment definition) or until they experienced major bleeding. Pa-

tients were not censored for reasons other than major bleeding or study drug discontinuation.

Univariate Cox regression modeling was used to estimate the hazard ratios (HRs) and 95% confidence intervals for individual risk factors with major bleeding as the dependent variable. All potential risk factors investigated in the univariate analyses were included in the multivariate Cox regression analyses; only those variables with p values that remained significant at the 5% level in the presence of other selected variables were retained in the final model. *c*-statistics were estimated to quantify the predictive accuracy of the risk schemes, with 95% confidence intervals obtained by bootstrapping analyses. The Hosmer-Lemeshow test for calibration was also performed whenever a *c*-statistic was calculated. All analyses were performed using SAS statistical software (version 8.2, SAS Institute, Inc., Cary, North Carolina). More detailed descriptions of the analytical methods used for the SPORTIF III and V trials are published elsewhere (17,18).

Results

Baseline characteristics of AF patients with known status regarding major bleeding during follow-up are summarized in Table 2. Patients in the whole cohort experiencing major bleeding events (n = 217) were more often elderly (p < 0.0001), nonsmokers (p = 0.016) with diabetes (p = 0.018), LV dysfunction (p = 0.018), previous stroke or transient ischemic attack (p < 0.0001), and impaired renal function (p < 0.0001). As expected, those with bleeding events had a higher mean CHADS$_2$ score than those without bleeding events (p < 0.0001).

Among the 7,329 patients, 79% were previously receiving vitamin K antagonist treatment, whereas 21% were vitamin K antagonist naive. Among those previously receiving vitamin K antagonist treatment, 46% had their AF diagnosed >5 years ago, 16% between 1 and 5 years, and the remaining 38% within the preceding year. The overall mean (SD) for the number of days in the on-treatment analysis

Table 2	**Baseline Characteristics of Atrial Fibrillation Patients With Known Follow-up Status Regarding Major Bleeding**		
Characteristic	**Bleeding Event (n = 234)**	**No Bleed (n = 7,095)**	**p Value**
Age, yrs, mean (SD)	73.9 (8.6)	70.9 (8.9)	<0.0001
>65	196 (84)	5,349 (75)	0.0031
≥75	125 (53)	2,679 (38)	<0.0001
Female sex	73 (31)	2,184 (31)	0.89
Body mass index, kg/m^2	28.7 (6.6)	29.0 (5.8)	0.50
AF type			
Duration since first diagnosed (yrs)	6.4 (5.9)	6.3 (7.1)	0.91
Paroxysmal	26 (11)	810 (12)	1.00
Persistent/permanent	208 (89)	6,282 (88)	1.00
Medical history			
Hypertension	180 (77)	5445 (77)	1.00
Diabetes mellitus	67 (29)	1658 (23)	0.071
Coronary artery disease	117 (50)	3162 (45)	0.11
LV dysfunction	102 (44)	2579 (36)	0.027
Stroke/TIA	61 (26)	1478 (21)	0.060
SEEs	8 (3)	320 (5)	0.52
CHADS$_2$ score, mean (SD)	2.6 (1.2)	2.2 (1.2)	<0.0001
Bleeding risk factors			
Previous clinically significant bleed	19 (8)	441 (6)	0.22
SBP at entry, mean (SD)	136 (19)	135 (18)	0.48
CrCl <50 ml/min	57 (24)	885 (13)	<0.0001
Alcohol use	97 (41)	3,230 (46)	0.23
Smoking	11 (5)	667 (9)	0.011

Values shown are n (%) unless otherwise indicated.

AF = atrial fibrillation; CHADS$_2$ = congestive heart failure, hypertension, age >75 years, diabetes mellitus and previous stroke or transient ischemic attack (doubled); CrCl = creatinine clearance; LV = left ventricular; SEEs = systemic embolic events; SBP = systolic blood pressure; TIA = transient ischemic attack.

was 499 (196) days; the corresponding results for patients without and with major bleeding were 503 (194) days and 380 (217) days, respectively.

Univariate and multivariate analyses of risk factors predictive of major bleeding are shown in Table 3. By univariate analysis, significant predictors of bleeding were concurrent aspirin use, reduced creatinine clearance (<50 ml/min), advanced age (75 years and older), diabetes mellitus, LV dysfunction, smoking, and previous stroke or transient ischemic attack. By multivariate analysis, significant predictors of bleeding were aspirin use (p < 0.001), renal impairment (p < 0.001), age 75 years and older (p = 0.0008), diabetes (p = 0.0089), and LV dysfunction (p = 0.041).

In Table 4, rates of major bleeding by HAS-BLED score are presented for the entire cohort and for patients assigned to warfarin therapy. *c*-statistics for prediction of major bleeding were similar (0.66 and 0.67; p$_{trend}$ <0.0001 for both). The relationship between the individual components of the HAS-BLED scheme and clinical bleeding events is shown in Tables 5 and 6. Labile INR, advanced age, concomitant aspirin or nonsteroidal anti-inflammatory drug use were consistently predictive of major bleeding in this cohort.

Comparison of contemporary bleeding risk stratification schemas revealed variable classification of AF patients into various bleeding risk strata (Table 7). In this analysis, there was no significant difference in c statistics between patients in the warfarin arms compared with those in the ximelagatran arms of the SPORTIF trials. Among those treated with warfarin, the HAS-BLED scheme exhibited a marginally better *c*-statistic value (0.67) than the other 4 schemas evaluated, with the lowest *c*-statistic (0.50) associated with the scheme of Kuijer et al. (9). The HAS-BLED scheme classified 20.4% of the cohort into the low-risk category, with a bleeding rate of <1% per year, whereas subjects classified as low risk by the other schemes had higher bleeding rates (>1.9% per year). Among patients who were warfarin naive at entry (n = 769) and in those treated with

Table 3	**Risk Factors for Major Bleeding by Univariate and Multivariate Analyses**					
	Event Rate (%/Patient-Year)		**Univariate Analyses**		**Multivariate Analyses***	
	Risk Factor Present					
Risk Factor	**Yes**	**No**	**HR (95% CI)†**	**p Value**	**HR (95% CI)†**	**p Value**
Aspirin use	3.94	1.94	2.02 (1.54–2.65)	<0.0001	1.92 (1.40–2.51)	<0.0001
CrCl <50 ml/min	4.91	2.01	2.48 (1.84–3.35)	<0.0001	1.90 (1.38–2.62)	<0.0001
Age ≥75 yrs	3.42	1.73	1.97 (1.53–2.55)	<0.0001	1.71 (1.30–2.25)	0.0001
Diabetes mellitus	2.95	2.17	1.36 (1.02–1.80)	0.035	1.36 (1.03–1.81)	0.033
LV dysfunction	2.85	2.07	1.37 (1.06–1.77)	0.017	1.31 (1.01–1.70)	0.043
Smoking	1.20	2.47	0.49 (0.26–0.89)	0.019		
Previous stroke or TIA	3.05	2.18	1.40 (1.04–1.87)	0.024		
Coronary artery disease	2.65	2.11	1.25 (0.97–1.62)	0.083		
Clinically significant bleeding	3.15	2.30	1.36 (0.85–2.18)	0.19		
Alcohol abuse	2.14	2.53	0.84 (0.65–1.09)	0.20		
Statin use	2.08	2.48	0.84 (0.63–1.11)	0.22		
Female	2.41	2.32	1.04 (0.79–1.37)	0.79		
Hypertension	2.36	2.33	1.01 (0.75–1.37)	0.94		

*Only factors associated with p < 0.05 in the presence of other selected variables were retained in the final model. †HR (95% CI) derived by Cox regression modeling.

CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 2.

Table 4	Major Bleeding Rates by HAS-BLED Score in the Overall SPORTIF Cohort (n = 7,329) and Those Taking Warfarin Only (n = 3,665)			
HAS-BLED Score	Patients With Particular Score in the Whole Cohort*	Major Bleeding Events†	Patients With Particular Score Among Those Taking Warfarin Only*	Major Bleeding Events†
0	1,757 (24.0)	21 (1.2)	746 (20.4)	7 (0.9)
1	2,717 (37.1)	75 (2.8)	1,283 (35.0)	44 (3.4)
2	1,752 (23.9)	63 (3.6)	950 (25.9)	39 (4.1)
3	834 (11.4)	50 (6.0)	483 (13.2)	28 (5.8)
4	241 (3.3)	23 (9.5)	180 (4.9)	16 (8.9)
5	27 (0.4)	2 (7.4)	22 (0.6)	2 (9.1)
6	1 (0.0)	0	1 (0.0)	0
	c-statistic = 0.654; p value for trend <0.0001		*c*-statistic = 0.659; p value for trend <0.0001	

Values are n (%). *Percentage of column total. †Percentage of row total.

HAS-BLED = Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly; SPORTIF = Stroke Prevention Using an ORal Thrombin Inhibitor in Atrial Fibrillation.

warfarin plus aspirin concurrently (n = 772), the HAS-BLED schema displayed the highest *c*-statistic values (0.68 and 0.60, respectively) of the 5 risk schemas evaluated.

We also tested, with multivariate Cox regression models, whether the new score adds significantly to models already incorporating the 4 older scores 1 at a time. In all 4 instances, HAS-BLED was associated with p < 0.0001 when inserted into models already incorporating the older scores. In contrast, none of the other 4 older scores added significantly when inserted 1 at a time into a model already including HAS-BLED (full data not shown). The Hosmer-Lemeshow test for calibration was also performed in conjunction with all c statistics reported in Tables 7 and 8. None of the p values were <0.05 for any of the risk scores (i.e., lack of goodness of fit was not indicated). For HAS-BLED, for example, the p values were 0.24 for all patients and 0.13 for the warfarin patient cohort. For the schema by Shireman et al. (6) (the only one with a p value <0.1), the p value was 0.075 for the warfarin patients (and 0.29 for all patients) (complete data not shown).

There was a progressive increase in the HR for bleeding from the low-risk to moderate-risk stratum and from the moderate-risk to the high-risk stratum according to the HAS-BLED scheme (Table 8) that was less apparent with the other bleeding risk schemas.

Discussion

This analysis of the performance of various bleeding risk stratification schemas over >11,000 patient-years of anti-coagulation exposure confirms the predictive value of previously identified risk factors, including advanced patient age, concomitant use of aspirin or nonsteroidal anti-inflammatory drugs during anticoagulation use, and renal impairment. In addition, the data identify associations of diabetes mellitus and clinical heart failure or LV systolic dysfunction with an increased risk of bleeding during therapeutic anticoagulation in this particular cohort of patients with AF. Of the various risk stratification schemas evaluated, the HAS-BLED schema more accurately discriminated patients on the basis of bleeding risk, based on the magnitude of the c statistic.

Risk factors for bleeding with OAC have largely been derived from cohort studies or secondary analyses of clinical

Table 5	Risk Factors for Major Bleeding According to the HAS-BLED Score: Whole Cohort (n = 7,329)							
Risk Factor	SPORTIF III/V Cohort Definition	Risk Factors Present, n (%)	Major Bleeding		Univariate Analyses		Multivariate Analyses	
			With Risk Factors, n (%)	Without Risk Factors, n (%)	HR (95% CI)	p Value	HR (95% CI)	p Value
Hypertension	SBP >160 mm Hg at entry	533 (7.3)	19 (3.6)	215 (3.2)	1.14 (0.71–1.82)	0.59	1.10 (0.69–1.76)	0.70
Abnormal renal function*	CrCl <50 ml/min	942 (12.9)	57 (6.0)	177 (2.8)	2.48 (1.84–3.35)	<0.0001	1.77 (1.28–2.44)	0.0005
Stroke before entry	Yes/no	918 (12.5)	35 (3.8)	199 (3.1)	1.32 (0.92–1.89)	0.13	1.24 (0.87–1.78)	0.23
Bleeding history	History of clinically significant bleeding	460 (6.3)	19 (4.1)	215 (3.1)	1.36 (0.85–2.18)	0.19	1.31 (0.82–2.09)	0.26
Labile INR	TTR <60%	1,235 (33.7)	65 (5.3)	71 (2.9)	2.14 (1.53–2.99)	<0.0001	2.05 (1.54–2.74)	<0.0001
Elderly	Age >75 yrs at entry	2,441 (33.3)	116 (4.8)	118 (2.4)	2.10 (1.63–2.72)	<0.0001	1.76 (1.34–2.33)	<0.0001
	Age >65 yrs at entry	5,545 (75.7)	196 (3.5)	38 (2.1)	1.74 (1.23–2.47)	0.0017		
Drugs†	Aspirin or NSAID	3,051 (41.6)	136 (4.5)	98 (2.3)	1.92 (1.48–2.49)	<0.0001	1.85 (1.43–2.40)	<0.0001
Alcohol	Alcohol >20 U/week	204 (2.8)	6 (2.9)	228 (3.2)	1.00 (0.44–2.25)	1.00	1.11 (0.49–2.51)	0.80
Aspirin use	Aspirin at any time	1,578 (21.5)	80 (5.1)	154 (2.7)	2.02 (1.54–2.65)	<0.0001		
NSAID	NSAID at any time	1,956 (26.7)	89 (4.6)	145 (2.7)	1.58 (1.21–2.06)	0.0007		

*Abnormal liver function was an exclusion criterion for these studies. †Concomitant use of clopidogrel was not allowed.

NSAID = nonsteroidal anti-inflammatory drug; other abbreviations as in Tables 1, 2, 3, and 4.

Table 6 Risk Factors for Major Bleeding According to the HAS-BLED Score: Warfarin Patients Only (n = 3,665)

Risk Factor	SPORTIF III/V Cohort Definition	Risk Factors Present, n (%)	Major Bleeding		Univariate Analyses		Multivariate Analyses	
			With Risk Factors, n (%)	Without Risk Factors, n (%)	HR (95% CI)	p Value	HR (95% CI)	p Value
Hypertension	SBP >160 mm Hg at entry	260 (7.1)	7 (2.7)	129 (3.8)	0.69 (0.32–1.47)	0.34	0.65 (0.30–1.39)	0.27
Abnormal renal function*	CrCl <50 ml/min	488 (13.4)	31 (6.4)	105 (3.3)	2.15 (1.44–3.21)	0.0002	1.46 (0.95–2.26)	0.085
Stroke before entry	Yes/no	450 (12.3)	18 (4.0)	118 (3.7)	1.17 (0.71–1.92)	0.53	1.12 (0.68–1.84)	0.66
Bleeding history	History of clinically significant bleeding	208 (5.7)	10 (4.8)	126 (3.6)	1.32 (0.69–2.51)	0.40	1.31 (0.68–2.49)	0.42
Labile INR	TTR <60%	1,235 (33.7)	65 (5.3)	71 (2.9)	2.14 (1.53–2.99)	<0.0001	2.06 (1.47–.89)	<0.0001
Elderly	Age >75 yrs at entry	1,222 (33.3)	67 (5.5)	69 (2.8)	2.07 (1.48–2.89)	<0.0001	1.82 (1.27–2.62)	0.0012
	Age >65 yrs at entry	2,762 (75.4)	112 (4.1)	24 (2.7)	1.57 (1.01–.44)	0.044		
Drugs†	Aspirin or NSAID	1,487 (40.6)	79 (5.3)	57 (2.6)	2.06 (1.47–2.90)	<0.0001	1.96 (1.39–2.76)	0.0001
Alcohol	Alcohol >20 U/week	99 (2.7)	3 (3.0)	133 (3.7)	0.89 (0.28–2.78)	0.84	1.00 (0.32–3.17)	0.99
Aspirin use	Aspirin at any time	772 (21.1)	50 (6.5)	86 (3.0)	2.39 (1.69–3.39)	<0.0001		
NSAID	NSAID at any time	954 (26.0)	50 (5.2)	86 (3.2)	1.59 (1.12–2.25)	0.0093		

*Abnormal liver function was an exclusion criterion for these studies. †Concomitant use of clopidogrel was not allowed.
Abbreviations as in Tables 1, 2, 3, 4, and 5.

trial data. A systematic review of the literature confined to AF populations identified advanced age, uncontrolled hypertension, ischemic heart disease, cerebrovascular disease, anemia, concomitant antiplatelet therapy, and previous bleeding as predictors of major bleeding events during anticoagulation (19), and labile INR control, advanced patient age, and concomitant aspirin or nonsteroidal anti-inflammatory drug use have been consistently identified as predictors in other analyses (10). Diabetes mellitus, controlled hypertension, and sex were not significant risk factors for bleeding in the systematic review forming the basis for the UK-NICE clinical practice guidelines (19). Other factors specifically associated with an incremental risk of intracerebral hemorrhage during OAC include associated

cerebrovascular disease and concomitant antiplatelet therapy; tobacco use or alcohol consumption; ethnicity; genotype; certain vascular abnormalities, such as amyloid angiopathy, leukoaraiosis, and microbleeds detected by brain imaging; and possibly genetic variations (20). Thus, the bleeding risk associated with diabetes mellitus and clinical heart failure or LV systolic dysfunction in anticoagulated AF populations requires further study.

Of note, many of the risk factors for anticoagulation-related bleeding are also indications for the use of anticoagulants in AF patients (10,14,15,19). Patients in whom major bleeding complications developed during anticoagulation therapy had a higher mean CHADS$_2$ score than those without bleeding, consistent with previous observa-

Table 7 Predictive Value of Contemporary Bleeding Risk Schemas in Patients Taking Warfarin Compared With the Whole Study Cohort and Subgroups of Warfarin-Naive Patients and Those Taking Warfarin Plus Aspirin

Bleeding Risk Score (Ref. #)	Warfarin Patients (n = 3,665)				c-Statistic* (95% CI)		
	Low	Moderate	High	c-Statistic* (95% CI)	All Patients (n = 7,329)	Warfarin-Naive Patients at Baseline (n = 769)	Patients Taking Warfarin + Aspirin (n = 772)
HAS-BLED (16)					0.65 (0.61–0.68)	0.66 (0.55–0.74)	0.60 (0.53–0.68)
% in risk category	20.4	60.9	18.7	0.66			
Bleeding events, n (%)†	7 (0.9)	83 (3.7)	46 (6.7)	(0.61–0.70)			
Shireman et al. (6)					0.64 (0.61–0.68)	0.61 (0.52–0.71)	0.58 (0.51–0.66)
% in risk category	82.2	17.7	0.1	0.63			
Bleeding events, n (%)	99 (3.3)	37 (5.7)	0 (0.0)	(0.58–0.67)			
HEMORR$_2$HAGES (7)					0.62 (0.58–0.65)	0.62 (0.52–0.72)	0.58 (0.51–0.66)
% in risk category	73.5	23.8	2.7	0.61			
Bleeding events, n (%)	81 (3.0)	53 (6.1)	2 (2.0)	(0.56–0.65)			
Beyth et al. (8)					0.57 (0.53–0.60)	0.50 (0.44–0.57)	0.52 (0.46–0.57)
% in risk category	10.2	79.6	10.2	0.56			
Bleeding events, n (%)	8 (2.1)	113 (3.9)	15 (4.0)	(0.51–0.60)			
Kuijer et al. (9)					0.49 (0.46–0.52)	0.44 (0.38–0.51)	0.49 (0.45–0.55)
% in risk category	9.0	85.7	5.3	0.52			
Bleeding events, n (%)	11 (3.0)	120 (3.8)	5 (2.6)	(0.48–0.56)			

*All c-statistics have been calculated based on the entire range for each risk score. †Bleeding rates are per patient.
Abbreviations as in Tables 1, 3, and 4.

Table 8	**Hazard Ratios (95% Confidence Interval) of Risk Categories for the 5 Bleeding Risk Stratification Schemas Among Warfarin Patients (n = 3,665)**		
Schema (Ref. #)	Moderate vs. Low	High vs. Moderate	High vs. Low
HAS-BLED (16)			
HR (95% CI)	4.31 (1.99–9.33)	2.02 (1.41–2.90)	8.56 (3.86–18.98)
p value	0.0002	0.0001	<0.0001
Shireman et al. (6)			
HR (95% CI)	1.87 (1.28–2.72)	—	—
p value	0.0012		
HEMORR$_2$HAGES (7)			
HR (95% CI)	2.19 (1.55–3.10)	0.34 (0.08–1.38)	0.75 (0.18–3.06)
p value	<0.0001	0.13	0.69
Beyth et al. (8)			
HR (95% CI)	1.87 (0.91–3.82)	1.10 (0.64–1.89)	2.07 (0.88–4.90)
p value	0.09	0.73	0.096
Kuijer et al. (9)			
HR (95% CI)	1.17 (0.63–2.16)	0.67 (0.27–1.64)	0.78 (0.27–2.24)
p value	0.63	0.38	0.64

Abbreviations as in Tables 3, 4, and 7.

tions (14,15). It has been suggested that the CHADS$_2$ stroke risk stratification and the HEMORR$_2$HAGES bleeding risk scores are so closely correlated that they classify two-thirds of patients into similar risk strata for hemorrhagic and ischemic events, casting doubt on the clinical utility of combining the 2 schemas (21).

The available bleeding risk stratification schemas classify variable proportions of AF patients into low-, moderate-, and high-risk categories. In this respect, the HAS-BLED schema displayed better predictive power than the 4 other tested bleeding risk stratification methods for bleeding events among patients in the combined SPORTIF III and V cohort, as well as for those randomized to the adjusted-dose arms, the subgroup who were warfarin naive at entry and those taking aspirin concurrently with warfarin, based on comparative *c* statistics.

Optimum selection of patients with AF for anticoagulant therapy depends not only on assessment of their intrinsic risk of thromboembolism but also on identification of those at increased risk of the development of bleeding complications. Even in patients at moderate or intermediate risk of stroke, accurate identification of those at low risk of bleeding may guide a preference for anticoagulation over aspirin, given additional data showing that anticoagulation may be the better option for stroke prevention (22), with a net clinical benefit (even when considering potential bleeding risk) in favor of anticoagulation rather than antiplatelet therapy. Of patients enrolled in the SPORTIF trials by virtue of at least 1 stroke risk factor other than AF, approximately 1 in 5 were in the low-risk category for bleeding based on the HAS-BLED criteria, and major bleeding occurred at a rate of <1% per year in these cases during treatment. In contrast, patients classified as low risk by the other 4 schemas experienced higher rates of bleeding (>1.9% per year) during the same period. There was a

progressive increment in HR for bleeding from the lowest to highest risk strata delineated by the HAS-BLED schema, but this gradient was not verified for the other scales tested.

These findings in a large clinical trial cohort are broadly comparable to those in the initial validation of HAS-BLED in >3,000 patients with AF in the Euro Heart survey followed for 1 year (16). In that analysis, the HAS-BLED schema also displayed predictive accuracy (*c*-statistic = 0.72), outperforming other bleeding risk schemas in AF patients treated with platelet inhibitor drugs or without antithrombotic therapy (*c*-statistic = 0.91 and 0.85, respectively), indicating that bleeding risk estimated by this method is not confined to anticoagulated patients. Whether bleeding risk estimated by this method will also apply to patients treated with newer anticoagulant drugs, such as dabigatran, rivaroxaban, apixaban, and edoxaban currently under development for stroke prevention in patients with AF, has not been evaluated. Estimation of bleeding risk will likely be important with these new agents even if they show efficacy superior or noninferior to that of warfarin and similar or lower rates of major bleeding because prophylactic therapy could potentially be applied more broadly across the patient population at risk (22).

With particular reference to dabigatran, 2 doses of which were compared with warfarin in the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial (23), the availability of an accurate bleeding risk assessment tool could potentially prove valuable in dose selection for individual patients if combined with stroke risk assessment. Although it is appealing to think that the HAS-BLED schema could be effectively applied in this context, further validation of its predictive value for bleeding in relation to dabigatran dose would be necessary if the compound were approved and brought to market for routine clinical use.

Study limitations. Assessment of bleeding risk is complicated by variation in the criteria used to define major, clinically relevant nonmajor and minor bleeding events, although these have been more uniform in recent trials than in earlier studies (24). Furthermore, bleeding rates and risk factors derived from clinical trial populations in which patients are carefully selected according to specific research protocols, anticoagulated using standard drug supply sources and monitored with stable thromboplastin reagents by dedicated personnel according to rigid criteria, may differ from those in clinical practice. Also, many of the patients were not warfarin naive and bleeding risk prediction might be much better if it took into account the time-specific context of treatment, including when warfarin was started and recent experience (e.g., in the past month) with antiplatelet drugs and INR control, and whether it predicted risk of bleeding in the next month (rather than on average over the course of therapy); however, the addition of these variables would introduce such complexity and reduce practical utility for everyday clinical use.

Advancing age is a continuous variable linearly related to the risks of stroke and bleeding (19). In the clinical trial

cohort that formed the basis for this report, >75% of participants were older than 65 years of age and the elderly criterion for the HAS-BLED schema was taken as age 75 years and older at study entry. Setting this threshold at age 65 years would have a small effect on the results (shifting the *c* statistic from 0.67 to 0.65 for the 3,665 patients assigned to warfarin). Bleeding in elderly patients with AF is more related to biological age rather than chronological age and is often multifactorial, being affected by comorbidity, anticoagulation intensity and lability, and frequent changes in concomitant pharmacology (10,19,21). Also, in comparing the different prediction schemas, it is important to recognize that some include only risk factors that could be known at the time of starting warfarin, whereas 2 schemas (HAS-BLED and that of Shireman et al. [6]) include time-dependent risk factors. The HAS-BLED score already accounts for some of these variables, enhancing its predictive value as a cumulative assessment of bleeding risk.

Conclusions

This analysis identifies diabetes and LV dysfunction as potential clinical correlates of bleeding in an anticoagulated clinical trial cohort of patients with nonvalvular AF. The HAS-BLED score may be a useful assessment of bleeding risk in AF patients in everyday clinical practice.

Reprint requests and correspondence: Prof. Gregory Y. H. Lip, University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Dudley Road, Birmingham B18 7QH, England. E-mail: g.y.h.lip@bham.ac.uk.

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