Journal of Thrombosis and Haemostasis, **9**: 1460–1467 DOI: 10.1111/j.1538-7836.2011.04378.x

ORIGINAL ARTICLE

Bleeding risk in 'real world' patients with atrial fibrillation: comparison of two established bleeding prediction schemes in a nationwide cohort

J. B. OLESEN,* G. Y. H. LIP,† P. R. HANSEN,* J. LINDHARDSEN,* O. AHLEHOFF,* C. ANDERSSON,* P. WEEKE,* M. L. HANSEN,* G. H. GISLASON* and C. TORP-PEDERSEN*

**Department of Cardiology, Copenhagen University Hospital Gentofte, Hellerup, Denmark; and †University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, UK*

To cite this article: Olesen JB, Lip GYH, 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**: 1460–7.

Summary. *Background:* Oral anticoagulation (OAC) in patients with atrial fibrillation (AF) is a double-edged sword, because it decreases the risk of stroke at the cost of an increased risk of bleeding. We compared the performance of a new bleeding prediction scheme, HAS-BLED, with an older bleeding prediction scheme, $HEMORR_2HAGES$, in a cohort of 'real-world' AF patients. *Methods:* By individual-level-linkage of nationwide registers, we identified all patients (n = 118 584) discharged with non-valvular AF in Denmark during the period 1997–2006, with and without OAC. Major bleeding rates during 1 year of follow-up were determined, and the predictive capabilities of the two schemes were compared by c-statistics. The risk of bleeding associated with individual risk factors composing HAS-BLED was estimated using Cox proportional-hazard analyses. *Results:* Of AF patients receiving OAC (n = 44 771), 34.8% and 47.3% were categorized as 'low bleeding risk' by HAS-BLED and $HEMORR_2HAGES$, respectively, and the bleeding rates per 100 person-years were 2.66 (95% confidence interval [CI], 2.40–2.94) and 3.06 (2.83–3.32), respectively. C-statistics for the two schemes were 0.795 (0.759–0.829) and 0.771 (0.733–0.806), respectively. The risk factors composing HAS-BLED were associated with varying risks, with a history of bleeding (hazard ratio [HR] 2.98; 95% CI 2.68–3.31) and being elderly (HR 1.93; 95% CI 1.71–2.18) being associated with the highest risks. Comparable results were found in AF patients not receiving OAC (n = 77 813). *Conclusions:* In an unselected nationwide cohort of hospitalized patients with atrial fibrillation, the HAS-BLED score performs similarly to $HEMORR_2HAGES$ in predicting bleeding risk but HAS-BLED is much simpler and easier to use in everyday clinical practise.

Correspondence: Jonas B. Olesen, Department of Cardiology, Copenhagen University Hospital Gentofte, Post 635, Niels Andersens Vej 65, 2900 Hellerup, Denmark.
Tel.: +45 2361 7139; fax: +45 7020 1283.
E-mail: jo@heart.dk

Received 15 April 2011, accepted 23 May 2011

Keywords: atrial fibrillation, bleeding, cohort, epidemiology, risk scheme.

Introduction

The decision to treat patients with atrial fibrillation (AF) with oral anticoagulation (OAC) depends on the expected risk of both stroke and bleeding. Whilst several stroke risk stratification schemes have been developed for patients with AF [1–5], only two bleeding risk stratification schemes have been derived and validated in AF populations [6,7], while other bleeding risk schemes have been derived from studies of more heterogeneous populations of patients receiving OAC (of which only a proportion had AF) and then applied to AF populations [8–10].

The two bleeding prediction schemes derived and validated in patients with AF are the Hepatic or renal disease, Ethanol abuse, Malignancy, Older age, Reduced platelet count or function, Rebleeding risk, Hypertension, Anemia, Genetic factors, Excessive fall risk, Stroke ($HEMORR_2HAGES$) score and the recently developed Hypertension, Abnormal renal/liver function, Stroke, Bleeding history, Labile international normalized ratio (INR), Elderly, Drug consumption/alcohol abuse (HAS-BLED) score [6,7]. HAS-BLED was initially validated in a European AF cohort participating in the EuroHeart survey, where the performance of this scheme was good in the overall population, and especially in patients treated without OAC [7]. In addition, the performance of HAS-BLED has been tested in the anticoagulated patients that participated in the Stroke Prevention using an ORal Thrombin Inhibitor in atrial Fibrillation (SPORTIF) trial, where it was superior to $HEMORR_2HAGES$ and to other published bleeding prediction schemes, with a stepwise increase in rates of major bleeding

with increasing HAS-BLED score [11]. The predictive capabilities of HAS-BLED and HEMORR$_2$HAGES have not, however, been directly compared in a large 'real-world' AF patient cohort.

In Denmark, individual linkage of data from nationwide unselective registers makes it possible to validate and compare such bleeding risk stratification schemes in real-world AF patients with and without OAC. The first objective of this study was to evaluate the predictive capability of HAS-BLED and compare it with the predictive capability of HEMORR$_2$HAGES. Secondly, we investigated the bleeding risk attributable to individual factors composing HAS-BLED.

Methods

Registry data sources

In Denmark, all citizens have a permanent and personal registration number, which enables individual level-linkage of nationwide registries. Since 1978, the Danish National Patient Registry has registered all admissions from Danish hospitals with one primary and, if appropriate, one or more secondary discharge diagnoses. Diagnoses are coded according to the International Classification of Diseases; the 8th revision (ICD-8) until 1994 and the 10th revision (ICD-10) from 1994 onwards [12]. From 1996 invasive therapeutic procedures (surgery, percutaneous interventions, etc.) have been coded according to the Nordic Medical Statistics Committees (NOMESKOs) Classification of Surgical Procedures (NCSP). The Danish Registry of Medicinal Product Statistics (prescription registry) holds accurate information on all prescriptions dispensed from Danish pharmacies since 1995; drugs are according to the international Anatomical Therapeutic Chemical (ATC) classification system [13]. The civil registration system holds information on vital status for all citizens, and the National Causes of Death Registry holds information on primary and contributing causes of death.

Study population

From the National Patient Registry, we identified all patients with non-valvular AF in the period 1997–2006. Non-valvular AF was defined by a discharge diagnosis of AF or atrial flutter (ICD10: I48), absence of previous diagnoses of mitral or aortic valve disease (ICD8: 394–396, 4240, 4241, and ICD10: I05, I06, I34, I35), and absence of mitral or aortic valve surgery (NCSP: KFK, KFM, KFP), as done previously [14,15]. Because pharmacotherapy may be changed or intensified in relation to hospitalization, follow-up was started 7 days after discharge from index AF hospitalization. Patients were excluded if they died or experienced a major bleeding episode in this 7 days quarantine period. Pharmacological treatment was identified by claimed prescriptions from 180 days before discharge to 7 days thereafter. The population was divided into an OAC cohort (i.e. patients treated with vitamin K antagonists [VKAs] [ATC: B01AA] and/or heparins [B01AB]), and a non-OAC cohort (Fig. 1). Patients were censored at time of death or at 1 year of follow-up.

The HAS-BLED score

The precise definitions of covariates in HAS-BLED are presented in Table S1. Hypertension was defined by claimed prescriptions of at least two of the following classes of antihypertensive drugs: adrenergic α antagonist, non-loop-diuretics, vasodilators, beta-blockers, calcium channel blockers, and renin-angiotensin system inhibitors. This definition of hypertension has previously been validated [14].

Abnormal renal/liver function was identified from diagnoses and therapeutic procedures in the National Patient Registry (i.e. patients with renal/liver cancer, chronic renal/liver disease, renal/liver surgery, dialysis, cirrhosis and hepatitis). Information on stroke was also obtained from the National Patient Registry. For stroke, we used previous diagnoses of peripheral artery embolism, ischemic stroke and transient ischemic attack as done previously [1,14,16]. Bleeding history was identified by previous major bleeding during hospitalization or bleeding leading to hospitalization [17,18]. Data on labile INR were not available. Elderly patients were patients aged > 65 years at discharge. Drug consumption was identified from claimed prescriptions of platelet inhibitors or non-steroidal anti-inflammatory drugs (NSAIDs), and alcohol abuse was identified from hospitalizations for diseases caused by alcohol or adverse alcohol consumption reported during hospitalization.

The HAS-BLED score was the sum of points obtained after adding one point for hypertension, abnormal renal function,

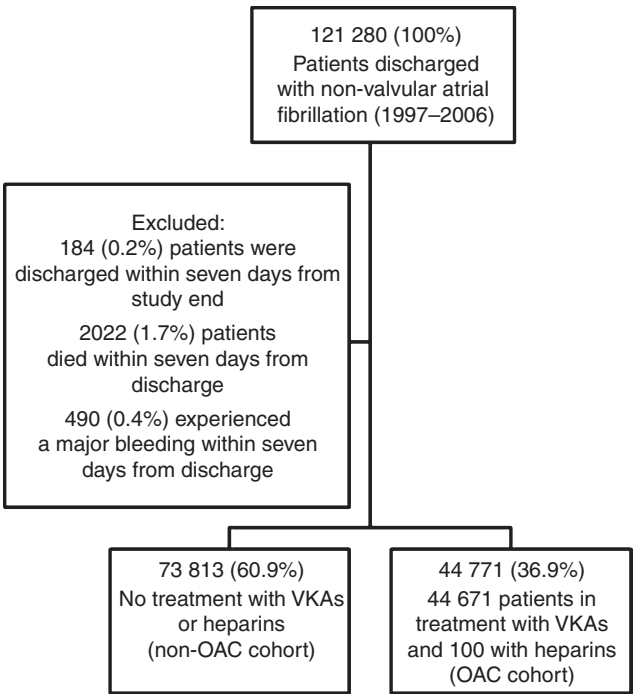

Fig. 1. Selection of study population. OAC, oral anticoagulation; VKA, vitamin K antagonist.

abnormal liver function, stroke, bleeding history, being elderly, drug consumption and alcohol abuse, thus this score ranged from 0 to 8 (and not 9 because we had no information on labile INR) [7]. Patients were categorized as 'low', 'intermediate' and 'high bleeding risk' according to HAS-BLED scores 0–1, 2 and ≥ 3, respectively.

The HEMORR$_2$HAGES score

The precise definitions of covariates in HEMORR$_2$HAGES are presented in Table S2. Hepatic or renal disease, ethanol abuse, re-bleeding risk (bleeding history), hypertension and stroke were defined as in HAS-BLED. Malignancy was identified by any diagnosis of cancer. Older age was for patients > 75 years at discharge. Reduced platelet count or function was determined from diagnosed coagulopathies. Anemia was determined from the corresponding diagnoses. As in the original article by Gage *et al.* [6] describing HEMORR$_2$HAGES, we had no information on genetic factors, and excessive fall risk was identified by diagnoses of dementia, Parkinson's disease, or psychiatric disease.

The HEMORR$_2$HAGES score was the sum of points after adding one point for hepatic or renal disease, ethanol abuse, malignancy, older age > 75 years, reduced platelet count or function, hypertension, anemia, excessive fall risk and stroke, and two points for rebleeding risk, thus this score ranged from 0 to 11 (and not 12 because we had no information on genetic factors) [6]. Patients were categorized as 'low', 'intermediate' and 'high bleeding risk' according to HEMORR$_2$HAGES scores 0–1, 2–3 and ≥ 4, respectively.

Outcome

The study outcome was hospitalization or death from major bleeding, including gastrointestinal bleeding, intracranial bleeding, bleeding from the urinary tract or airway bleeding (ICD10: I60–I62, I690–I692, J942, K250, K254, K260, K264, K270, K280, K920–K922, N02, R04, R31, S064–S066), as described previously [17,18]. Patients were censored at death due to other causes than bleeding or at 1 year of follow-up.

Statistical analysis

Comparisons of baseline characteristics between patients experiencing and not experiencing a major bleed during follow-up were performed by chi-square test and Students *t*-test for categorical and continuous covariates, respectively.

For both HAS-BLED and HEMORR$_2$HAGES, the rate of hospitalization or death from major bleeding during 1 year of follow-up was estimated for the three risk categories (i.e. 'low', 'intermediate' and 'high bleeding risk'). Unadjusted Cox proportional-hazard analyses estimated the risk associated with the 'intermediate' and 'high bleeding risk' categories, with the 'low bleeding risk' patients used as the reference. The negative predictive value (NPV) of 'low bleeding risk' was calculated for both schemes, dividing the number of patients not experiencing a major bleed with the number in the risk category.

The ability of HAS-BLED and HEMORR$_2$HAGES to predict major bleeding was assessed by c-statistics of unadjusted Cox regression models. Risk scores were first entered into the Cox model as continuous covariates, and secondly as categorical risk groups (i.e. 'low', 'intermediate' and 'high bleeding risk'), according to the method of Liu *et al.* [19].

In Cox proportional-hazard analyses, we calculated the bleeding risk associated with the individual risk factors composing HAS-BLED. Furthermore, with age < 60 years used as the reference, we estimated the bleeding risk associated with each 5-year increment in patient age.

In the non-OAC cohort, curves of cumulative incidence of major bleeding based on competing-risks regression (i.e. counting of the competing risk of death) were constructed for the different HAS-BLED scores. A two-sided P-value < 0.05 was considered statistically significant. All analyses were performed with SAS statistical software version 9.1 (SAS Institute Inc., Cary, NC, USA) and STATA statistical software version 11.0 (StataCorp LP, College Station, TX, USA).

Ethics

No ethical approval is required for retrospective register studies in Denmark. The study was approved by The Danish Data Protection Agency (No. 2007-41-1667).

Results

In the 10-year study period we identified 118 584 patients with non-valvular AF, of whom 73 813 (60.9%) did not receive OAC at baseline (Fig. 1). During the 1 year of follow-up, 12.6% of the non-OAC cohort claimed at least one prescription for VKA, and censoring these patients at the time of VKA initiation did not alter the results of our analyses (data not shown).

Table 1 shows baseline characteristics for the whole study population of patients with non-valvular AF according to development of major bleeding during the 1-year follow-up, with the population divided into two cohorts according to OAC therapy. Subjects sustaining a major bleed were significantly older, more often male, and more likely to have heart failure, stroke, vascular disease, renal/liver disease, a history of bleeding, alcohol abuse, malignancy, reduced platelet count or function, and anemia. Whilst there were some differences in the proportions of drugs used between those with and without major bleeding, aspirin and NSAID use was more common in those sustaining bleeding events.

Table 2 summarizes major bleeding rates during the 1 year of follow-up, in relation to OAC therapy. HEMORR$_2$HAGES categorized 17.5% and 10.9% as 'high bleeding risk' in the non-OAC and OAC groups, respectively. HAS-BLED categorized an equal number of patients in the three risk categories. The rate of major bleeding increased with increasing risk category for both HAS-BLED and HEMORR$_2$HAGES, with compa-

Table 1 Baseline characteristics of patients with atrial fibrillation according to occurrence of major bleeding during follow-up

	Non-OAC cohort			OAC cohort		
	Major bleeding (n = 3029)	No major bleeding (n = 70 784)	P-value for difference	Major bleeding (n = 2051)	No major bleeding (n = 42 720)	P-value for difference
Age, mean (SD)	78.6 (10.6)	74.7 (13.6)	< 0.001	74.6 (9.2)	71.2 (10.7)	< 0.001
Male gender (%)	1715 (56.6)	34 219 (48.3)	< 0.001	1369 (66.8)	26 140 (61.2)	< 0.001
HAS-BLED score, mean (SD)	2.6 (1.2)	2.1 (1.2)	< 0.001	2.5 (1.2)	2.0 (1.2)	< 0.001
$HEMORR_2HAGES$ score, mean (SD)	2.9 (1.6)	2.1 (1.5)	< 0.001	2.4 (1.5)	1.7 (1.3)	< 0.001
Comorbidity (%)						
Heart failure	629 (20.8)	12 510 (17.7)	< 0.001	501 (24.4)	8460 (19.8)	< 0.001
Hypertension	1061 (35.0)	24 088 (34.0)	0.26	1059 (51.6)	21 127 (49.5)	0.05
Diabetes mellitus	278 (9.2)	6248 (8.8)	0.51	233 (11.4)	4044 (9.5)	0.004
Stroke	764 (25.2)	12 217 (17.3)	< 0.001	458 (22.3)	7433 (17.4)	< 0.001
Vascular disease	594 (19.6)	12 371 (17.5)	0.003	382 (18.6)	6333 (14.8)	< 0.001
Renal disease	293 (9.7)	4862 (6.9)	< 0.001	168 (8.2)	1971 (4.6)	< 0.001
Liver disease	293 (9.7)	4604 (6.5)	< 0.001	153 (7.5)	1840 (4.3)	< 0.001
Bleeding history	947 (31.3)	7706 (10.9)	< 0.001	464 (22.6)	3514 (8.2)	< 0.001
Alcohol abuse	166 (5.5)	3076 (4.4)	0.003	80 (3.9)	1198 (2.8)	0.004
Malignancy	606 (20.0)	11 472 (16.2)	< 0.001	301 (14.7)	4786 (11.2)	< 0.001
Reduced platelet count or function	1187 (39.2)	24 675 (34.9)	< 0.001	695 (33.9)	11 175 (26.2)	< 0.001
Anemia	381 (12.6)	5886 (8.3)	< 0.001	135 (6.6)	1668 (3.9)	< 0.001
Excessive fall risk	269 (8.9)	5626 (8.0)	0.06	70 (3.4)	1199 (2.8)	0.11
Concomitant medication (%)						
Adrenergic α-antagonist	50 (1.7)	962 (1.4)	0.18	40 (2.0)	638 (1.5)	0.10
Non-loop-diuretics	1006 (33.2)	20 744 (29.3)	< 0.001	724 (35.3)	13 919 (32.6)	0.01
Vasodilators	96 (3.2)	2243 (3.2)	1.00	60 (2.9)	1271 (3.0)	0.90
Beta blockers	911 (30.1)	25 318 (35.8)	< 0.001	1013 (49.4)	22 474 (52.6)	0.004
Calcium channel blockers	798 (26.4)	18 248 (25.8)	0.49	763 (37.2)	14 834 (34.7)	0.02
Renin-angiotensin system inhibitors	747 (24.7)	16 192 (22.9)	0.02	786 (38.3)	15 096 (35.3)	0.006
Loop-diuretics	1286 (42.5)	26 392 (37.3)	< 0.001	991 (48.3)	17 764 (41.6)	< 0.001
Statins	251 (8.3)	6699 (9.5)	0.03	334 (16.3)	6134 (14.4)	0.02
Antiplatelet drugs	1170 (38.6)	24 441 (34.5)	< 0.001	676 (33.0)	10 888 (25.5)	< 0.001
NSAID	704 (23.2)	15 083 (21.3)	0.01	468 (22.8)	8162 (19.1)	< 0.001
Digoxin	1455 (48.0)	30 009 (42.4)	< 0.001	1322 (64.5)	26 849 (62.9)	0.14
Amiodarone	67 (2.2)	1809 (2.6)	0.24	86 (4.2)	1865 (4.4)	0.71

AF, atrial fibrillation; NSAID, non-steroidal anti-inflammatory drug; OAC, oral anticoagulation.

Table 2 Major bleeding events during 1 year of follow-up in patients with atrial fibrillation, according to OAC treatment, risk category and bleeding prediction scheme

Risk category	n (%)	Bleeding (n)	Person-years (n)	Bleeding rate per 100 person-years (95% CI)
Non-OAC cohort				
HAS-BLED				
Low (score 0–1)	24 962 (33.8)	544	21 410	2.54 (2.34–2.76)
Intermediate (score 2)	23 143 (31.4)	1004	18 589	5.40 (5.08–5.75)
High (score ≥ 3)	25 708 (34.8)	1481	19 275	7.68 (7.30–8.08)
$HEMORR_2HAGES$				
Low (score 0–1)	28 049 (38.0)	613	24 725	2.48 (2.29–2.68)
Intermediate (score 2–3)	32 846 (44.5)	1419	25 674	5.53 (5.25–5.82)
High (score ≥ 4)	12 918 (17.5)	997	8875	11.23 (10.56–11.95)
Overall	73 813 (100)	3029	59 274	5.11 (4.93–5.30)
OAC cohort				
HAS-BLED				
Low (score 0–1)	15 570 (34.8)	377	14 172	2.66 (2.40–2.94)
Intermediate (score 2)	14 933 (33.4)	721	13 015	5.54 (5.15–5.96)
High (score ≥ 3)	14 268 (31.9)	953	11 749	8.11 (7.61–8.64)
$HEMORR_2HAGES$				
Low (score 0–1)	21 185 (47.3)	592	19 320	3.06 (2.83–3.32)
Intermediate (score 2–3)	18 713 (41.8)	1006	15 893	6.33 (5.95–6.73)
High (score ≥ 4)	4873 (10.9)	453	3724	12.16 (11.09–13.34)
Overall	44 771 (100)	2051	38 937	5.27 (5.04–5.50)

CI, confidence interval; HAS-BLED and $HEMORR_2HAGES$, see text; OAC, oral anticoagulation.

rable overall bleeding rates in the non-OAC and OAC cohorts (5.11 vs. 5.27 per 100 patient-years, respectively). The NPV of 'low bleeding risk' categorized by HAS-BLED was 97.8% and 97.6% without and with OAC, respectively, and the NPV of 'low bleeding risk' according to HEMORR$_2$HAGES was 97.8% and 97.2%, respectively.

Table 3 displays the major bleeding risk associated with the 'intermediate' and 'high bleeding risk' categories compared with the 'low bleeding risk' category according to the two bleeding prediction schemes in patients with or without OAC. In general, the difference in bleeding risk was more uniform between the risk categories of HAS-BLED and, specifically, the risk increase between the 'intermediate' and 'high bleeding risk' categories was less steep for HAS-BLED than for HEMORR$_2$HAGES.

Table 4 demonstrates c-statistics from Cox regression models. When risk scores were analysed as continuous covariates in the non-OAC cohort, c-statistics were 0.806 and 0.758 for HAS-BLED and HEMORR$_2$HAGES, respectively. The pattern was the same for the ability of the risk prediction schemes to categorize patients into the three risk categories. In the OAC cohort, the results were similar. Based on the point estimate, the analyses were suggestive of a better bleeding prediction capability of HAS-BLED compared with HEMORR$_2$HAGES, but there was overlap of the 95% confidence intervals for the two c-statistics.

Table 5 displays the risk factors composing HAS-BLED and their associated risk of major bleeding. In both the non-OAC and the OAC cohort, stroke, bleeding history, being elderly, drug consumption and alcohol abuse were significantly associated with major bleeding. Hypertension and abnormal renal function were not associated with bleeding in the non-OAC cohort, and hypertension and abnormal liver function were not associated with bleeding in the OAC cohort. The risk factor associated with the highest risk of bleeding was a history of bleeding (hazard ratio [HR] 2.98 and 3.43), followed by being elderly (HR 1.93 and 2.11). Figure 2 illustrates that the increase in major bleeding risk associated with age ≥ 60 years was not uniform, and in the non-OAC cohort the HR increased from 1.65 in patients aged 60–65 years to 3.09 in patients aged ≥ 85 years.

Figure 3 shows the cumulative incidence curves for major bleeding in the non-OAC cohort based on competing-risks regression. The higher bleeding rate in subjects with high HAS-BLED scores was clearly demonstrated (*P*-value for trend < 0.001). The curve for HAS-BLED score 8 was omitted because only two patients were in this category.

Table 3 Hazard ratio (95% CI) of major bleeding according to bleeding risk category

	Low (reference)	Moderate	High
Non-OAC cohort			
HAS-BLED	1.00	2.10 (1.89–2.33)	2.95 (2.68–3.26)
HEMORR$_2$HAGES	1.00	2.18 (1.99–2.40)	4.34 (3.92–4.80)
OAC cohort			
HAS-BLED	1.00	2.07 (1.83–2.34)	3.00 (2.67–3.38)
HEMORR$_2$HAGES	1.00	2.04 (1.85–2.26)	3.87 (3.43–4.38)

Results from unadjusted Cox proportional-hazard analyses.
CI, confidence interval; HAS-BLED and HEMORR$_2$HAGES, see text; OAC, oral anticoagulation.

Table 4 Bleeding predictive ability of HAS-BLED and HEMORR$_2$HAGES

	C-value (95% confidence interval)
Continuous scores*	
Non-OAC cohort	
HAS-BLED	0.806 (0.777–0.833)
HEMORR$_2$HAGES	0.758 (0.727–0.788)
OAC cohort	
HAS-BLED	0.795 (0.759–0.829)
HEMORR$_2$HAGES	0.771 (0.733–0.806)
Categorical risk categories†	
Non-OAC cohort	
HAS-BLED	0.815 (0.786–0.842)
HEMORR$_2$HAGES	0.769 (0.738–0.798)
OAC cohort	
HAS-BLED	0.795 (0.759–0.829)
HEMORR$_2$HAGES	0.782 (0.745–0.816)

C-statistics based on Cox regression models. HAS-BLED and HEMORR$_2$HAGES, see text; OAC, oral anticoagulation.
*The HAS-BLED score (0–8) and HEMORR$_2$HAGES score (0–11), respectively, analyzed as a continuous covariate.
†Risk categories (i.e. low, intermediate and high bleeding risk) analyzed as categorical covariates.

Discussion

This is the largest study comparing the HAS-BLED and HEMORR$_2$HAGES scores, which are two commonly used schemes developed to predict major bleeding in patients with non-valvular AF, and was based on a large unselected 'real world' nationwide cohort of patients. We found that HAS-BLED and HEMORR$_2$HAGES performed broadly similarly in predicting major bleeding, but a substantial advantage of HAS-BLED is its relative simplicity, which also allows ease of use in everyday clinical practise. Indeed, HAS-BLED was recently included in the European Society of Cardiology guidelines on treatment of patients with AF [20], as well as the Canadian Cardiovascular Society AF guidelines [21].

The covariates in the present study that were significant predictors of major bleeding could be categorized into 'increased bleeding predisposition' (that is, bleeding history, malignancy, reduced platelet count or function, and anemia), as well as heart failure, alcohol use, aspirin/NSAID use, and renal/liver disease. In agreement with Ho *et al.* [22], we found that hypertension *per se* was not a significant predictor of bleeding, but in the current study we relied on treated (and therefore potentially well-controlled) hypertension, which may be less of a predictive factor for bleeding. The literature on risk of bleeding with uncontrolled hypertension is inconclusive but systematic reviews suggest that poorly

Table 5 Hazard ratio of major bleeding associated with the risk factors of HAS-BLED in patients with atrial fibrillation according to anticoagulation status

HAS-BLED risk factor	*n* (%)	Hazard ratio (95% confidence interval)	*P*-value
Non-OAC cohort			
Hypertension	25 149 (34.1)	0.95 (0.88–1.02)	0.14
Abnormal renal function	5155 (7.0)	0.97 (0.76–1.23)	0.79
Abnormal liver function	4897 (6.6)	1.46 (1.15–1.85)	0.002
Stroke	12 981 (18.6)	1.35 (1.24–1.46)	< 0.001
Bleeding history	8653 (11.7)	3.43 (3.17–3.71)	< 0.001
Elderly > 65 years	57 576 (78.0)	2.11 (1.88–2.36)	< 0.001
Drug consumption	35 746 (48.4)	1.13 (1.05–1.21)	0.001
Alcohol abuse	3242 (4.4)	1.32 (1.13–1.55)	< 0.001
OAC cohort			
Hypertension	22 186 (49.6)	1.01 (0.93–1.11)	0.78
Abnormal renal function	2139 (4.8)	1.53 (1.14–2.05)	0.005
Abnormal liver function	1993 (4.5)	1.11 (0.82–1.51)	0.49
Stroke	7891 (17.6)	1.15 (1.03–1.28)	0.01
Bleeding history	3978 (8.9)	2.98 (2.68–3.31)	< 0.001
Elderly > 65 years	32 637 (72.9)	1.93 (1.71–2.18)	< 0.001
Drug consumption	17 794 (39.7)	1.38 (1.27–1.51)	< 0.001
Alcohol abuse	1278 (2.9)	1.53 (1.22–1.92)	< 0.001

Results from Cox proportional-hazard analyses. HAS-BLED, see text; OAC, oral anticoagulation.

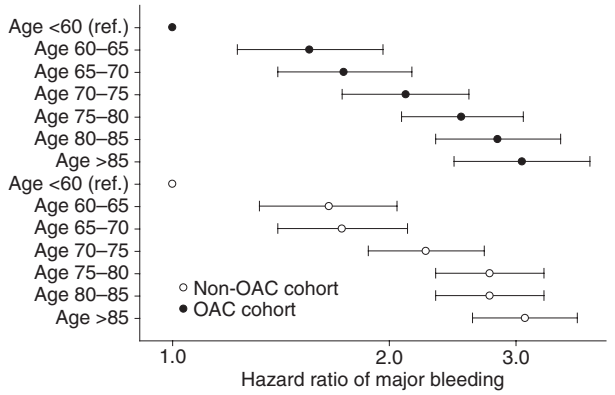

Fig. 2. Risk of major bleeding associated with increasing age in patients with non-valvular atrial fibrillation. OAC, oral anticoagulation.

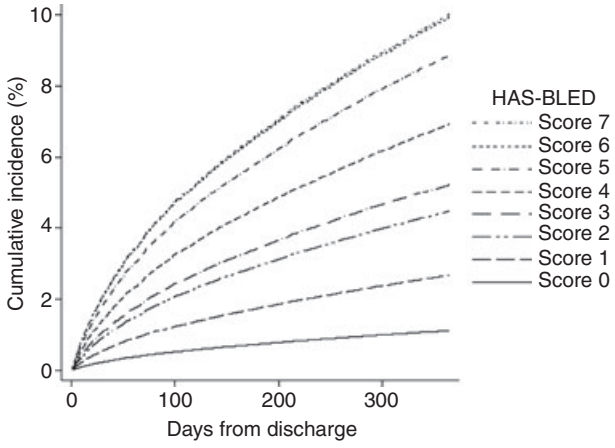

Fig. 3. Cumulative incidence of bleeding by HAS-BLED score. Result from competing-risks regression (i.e. counting for the competing risk of death) in the non-OAC cohort.

controlled blood pressure is an independent risk factor of bleeding [23]. Unsurprisingly, the risk factor with the highest hazard ratio for new major bleeding was a positive bleeding history, followed by an increase in age. The impact of the latter was also evident in previous analyses [24,25], and we found the risk to increase from 60 years of age. It is important to emphasize that with increasing age the risk of stroke also increases; indeed, OAC should not be avoided in elderly patients because of concerns regarding bleeding risk due to age alone, and the decision should always be based on careful evaluation of the balance between risk and benefit of OAC [20,26].

Our data clearly demonstrate an increasing bleeding rate with increasing HAS-BLED score, irrespective of OAC use. As expected, the bleeding rate with OAC was only slightly increased, because the prescription registry represents the selected population of patients that physicians considered to have acceptable risk of bleeding with OAC. This difference between the non-OAC and OAC cohorts was also evident in the baseline characteristics of patients (i.e. the non-OAC cohort had more comorbidities and received less medical treatment) (Table 1).

Clinical risk prediction scores need to be simple, easily memorized and practical to use. Thus, the use of HAS-BLED would help clinicians to make an informed choice regarding decision making rather than relying on guesswork. When compared with $HEMORR_2HAGES$ (and other older schema [11]), the HAS-BLED score is much easier to use in everyday clinical practise given that the HAS-BLED acronym is shorter and more idiomatic. Furthermore, the common risk factors for bleeding included in the HAS-BLED score are easier to access for clinicians, compared with $HEMORR_2HAGES$. Also, this validation study has been successfully performed in a very large

'real world' cohort and does not use highly selected patients that have been included within randomized clinical trials [11,27].

Limitations

The main study limitation was inherent to its retrospective observational nature, but its strength is the large size of this nationwide cohort and that the PPV of the diagnosis of AF is very high (99%) in the registry [28]. However, inclusion of only hospitalized patients with AF is likely to have increased the proportion of patients that were at a higher risk of major bleeding. The study outcome was restricted to hospitalization or death related to gastrointestinal bleeding, intracranial bleeding, bleeding from the urinary tract, and airway bleeding, and the results cannot be applied to the risk of minor bleeding. Nonetheless, it is not possible to determine the gravity (or severity) of the investigated bleeding events when compared with an ischemic stroke, which may require potentially complex net clinical benefit analyses, which was not the objective of the present study. We had no information on the reasons for absence of OAC in the substantial proportion of patients with non-valvular AF. Also, we could not differentiate between paroxysmal, persistent and permanent AF, but we are unaware of data where bleeding is influenced by the temporal pattern of AF. The frequencies of risk factors in the study population could also be underestimated because we identified patients with heart failure, hypertension and diabetes from prescription claims and thus did not detect patients treated with diet control and lifestyle interventions alone. Also, alcohol abuse was detected from previous disease caused by alcohol consumption and by adverse alcohol intake reported in relation to a hospitalization. Furthermore, we were not able to investigate the full potential of the two bleeding prediction schemes because we had no information on labile INR and genetic factors, the latter being uncommonly determined in 'real world' clinical practise.

Conclusions

In a nationwide cohort of patients discharged after hospitalization for AF we found a clear association between the HAS-BLED score and risk of major bleeding leading to hospitalization or death. Not all risk factors of HAS-BLED were associated with the same risk, and a history of bleeding and increasing age conferred a greater risk of bleeding than other covariates. When predicting bleeding in patients with AF, HAS-BLED performs broadly similarly to HEMORR$_2$HAGES, but HAS-BLED has advantages in being much simpler and easier to use in everyday clinical practise.

Addendum

J. B. Olesen made primary contributions to data collection and analysis, interpretation of results, and writing of the manuscript. J. B. Olesen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. J. B. Olesen and G. Y. H. Lip wrote the first draft. G. Y. H. Lip, P. R. Hansen, G. H. Gislason and C. Torp-Pedersen contributed to the study conception and design. All authors contributed to interpretation of results, revising the manuscript critically for important intellectual content, and all approved the final manuscript.

Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Data used for the HAS-BLED score.
Table S2. Data used for the HEMORR$_2$HAGES score.

Please note: Wiley-Blackwell are not responsible for the content or functionality of any supporting materials supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.

References

1 Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest* 2010; **137**: 263–72.
2 Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 2001; **285**: 2864–70.
3 Hart RG, Pearce LA, McBride R, Rothbart RM, Asinger RW, the Stroke Prevention in Atrial Fibrillation (SPAF) Investigators. Factors associated with ischemic stroke during aspirin therapy in atrial fibrillation: analysis of 2012 participants in the SPAF I-III clinical trials. *Stroke* 1999; **30**: 1223–9.
4 Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. *Arch Intern Med* 1994; **154**: 1449–57.
5 Wang TJ, Massaro JM, Levy D, Vasan RS, Wolf PA, D'Agostino RB, Larson MG, Kannel WB, Benjamin EJ. A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the community: the Framingham Heart Study. *JAMA* 2003; **290**: 1049–56.
6 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**: 713–9.
7 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**: 1093–100.
8 Shireman TI, Mahnken JD, Howard PA, Kresowik TF, Hou Q, Ellerbeck EF. Development of a contemporary bleeding risk model for elderly warfarin recipients. *Chest* 2006; **130**: 1390–6.
9 Kuijer PM, Hutten BA, Prins MH, Buller HR. Prediction of the risk of bleeding during anticoagulant treatment for venous thromboembolism. *Arch Intern Med* 1999; **159**: 457–60.

10 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**: 91–9.
11 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**: 173–80.
12 Andersen TF, Madsen M, Jorgensen J, Mellemkjoer L, Olsen JH. The Danish National Hospital Register. A valuable source of data for modern health sciences. *Dan Med Bull* 1999; **46**: 263–8.
13 Gaist D, Sorensen HT, Hallas J. The Danish prescription registries. *Dan Med Bull* 1997; **44**: 445–8.
14 Olesen JB, Lip GY, Hansen ML, Hansen PR, Tolstrup JS, Lindhardsen J, Selmer C, Ahlehoff O, Olsen AM, Gislason GH, Torp-Pedersen C. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. *BMJ* 2011; **342**: d124.
15 Go AS, Hylek EM, Borowsky LH, Phillips KA, Selby JV, Singer DE. Warfarin use among ambulatory patients with nonvalvular atrial fibrillation: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. *Ann Intern Med* 1999; **131**: 927–34.
16 Krarup LH, Boysen G, Janjua H, Prescott E, Truelsen T. Validity of stroke diagnoses in a National Register of patients. *Neuroepidemiology* 2007; **28**: 150–4.
17 Hansen ML, Sorensen R, Clausen MT, Fog-Petersen ML, Raunso J, Gadsboll N, Gislason GH, Folke F, Andersen SS, Schramm TK, Abildstrom SZ, Poulsen HE, Kober L, Torp-Pedersen C. Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation. *Arch Intern Med* 2010; **170**: 1433–41.
18 Sorensen R, Hansen ML, Abildstrom SZ, Hvelplund A, Andersson C, Jorgensen C, Madsen JK, Hansen PR, Kober L, Torp-Pedersen C, Gislason GH. Risk of bleeding in patients with acute myocardial infarction treated with different combinations of aspirin, clopidogrel, and vitamin K antagonists in Denmark: a retrospective analysis of nationwide registry data. *Lancet* 2009; **374**: 1967–74.
19 Liu L, Forman S, Barton B. Fitting Cox model using PROC PHREG and beyond in SAS. SAS Global Forum 2009. Paper 236.
20 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 *et al*. 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**: 2369–429.
21 Cairns JA, Connolly S, McMurtry S, Stephenson M, Talajic M, Committee CCSAFG. 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.
22 Ho LY, Siu CW, Yue WS, Lau CP, Lip GY, Tse HF. Safety and efficacy of oral anticoagulation therapy in Chinese patients with concomitant atrial fibrillation and hypertension. *J Hum Hypertens* 2011; **25**: 304–10.
23 Hughes M, Lip GY. Risk factors for anticoagulation-related bleeding complications in patients with atrial fibrillation: a systematic review. *QJM* 2007; **100**: 599–607.
24 Fang MC, Chang Y, Hylek EM, Rosand J, Greenberg SM, Go AS, Singer DE. Advanced age, anticoagulation intensity, and risk for intracranial hemorrhage among patients taking warfarin for atrial fibrillation. *Ann Intern Med* 2004; **141**: 745–52.
25 Hylek EM, Singer DE. Risk factors for intracranial hemorrhage in outpatients taking warfarin. *Ann Intern Med* 1994; **120**: 897–902.
26 Marinigh R, Lip GY, Fiotti N, Giansante C, Lane DA. Age as a risk factor for stroke in atrial fibrillation patients: implications for thromboprophylaxis. *J Am Coll Cardiol* 2010; **56**: 827–37.
27 Hohnloser SH. Stroke prevention versus bleeding risk in atrial fibrillation: a clinical dilemma. *J Am Coll Cardiol* 2011; **57**: 181–3.
28 Frost L, Andersen LV, Vestergaard P, Husted S, Mortensen LS. Trend in mortality after stroke with atrial fibrillation. *Am J Med* 2007; **120**: 47–53.