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ORIGINAL ARTICLE

Clinical performance of bleeding risk scores for predicting major and clinically relevant non-major bleeding events in patients receiving warfarin

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Summary. *Background:* Oral anticoagulant therapy is associated with an increased risk of hemorrhage, which can be assessed by bleeding risk scores. We evaluated the performance of five validated scores for predicting major and clinically relevant non-major bleeding events in patients receiving warfarin. *Methods and results:* We conducted an ambispective, single-center cohort study of 321 consecutive patients enrolled in an academic anticoagulation clinic. The following scores were calculated: modified Outpatient Bleeding Risk Index, Contemporary Bleeding Risk Model, HEMORR$_2$HAGES (Hepatic or Renal Disease, Ethanol Abuse, Malignancy, Older Age, Reduced Platelet Count or Function, Re-Bleeding, Hypertension, Anemia, Genetic Factors, Excessive Fall Risk and Stroke), ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation), and HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile International Normalized Ratio, Elderly, Drugs/Alcohol). Main outcomes were major bleeding and a composite of major plus clinically relevant non-major bleeding. Incidence rates for all group were 3.8 (95% confidence interval [CI] 2.0–6.4) and 11.9 (95% CI 8.6–16.4) events per 100 patient-years for major bleeding and major plus clinically relevant non-major bleeding, respectively. Agreement among the five scores was low to moderate (Kendall's tau-b coefficients 0.22–0.54). For major bleeding, the *c*-statistics ranged from 0.606 to 0.735, whereas for major plus clinically relevant non-major bleeding, they ranged from 0.549 to 0.613. For all scores, the 95% CI for the *c*-statistics crossed 0.5 or was very close. Among high-risk patients, the hazard ratios for major bleeding ranged from 0.90 to 39.01, whereas for major plus clinically relevant non-major bleeding, they ranged from 1.52 to 8.71. For intermediate-risk patients, no score, except the Contemporary Bleeding Risk Model, produced statistically significant hazard ratios. *Conclusion:* The scores demonstrated poor agreement and low to moderate discriminatory ability. General clinical implementation of these scores cannot be recommended yet.

Keywords: bleeding; prognosis; risk; risk assessment; warfarin.

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Introduction

Oral anticoagulants have been in use for longer than 60 years for the primary and secondary prevention of thromboembolic complications, resulting in substantial reductions in the risk of venous thromboembolism (VTE) occurrence or recurrence [1,2]. In the case of patients with atrial fibrillation (AF), adjusted-dose warfarin has been shown to reduce the relative risk of ischemic stroke and all-cause mortality in high-risk patients, and current guidelines suggest a rather liberal use of anticoagulant prophylaxis [3–7].

However, despite their proven benefit, the use of oral anticoagulants is associated with an increased risk of major bleeding (MB) averaging 1% per year in VTE patients [8] or as high as 4.2–7% in data derived from

randomized trials or observational studies in AF [9–13]. Furthermore, the incidence of intracranial hemorrhage is estimated at 0.2% per year [9]. Therefore, a number of consensus statements have postulated the need for assessing the patient's bleeding risk prior to initiating oral anticoagulants [6,9]. In practice, this assessment has been based on the perceived risks and benefits for each patient, and therefore it might be highly variable and difficult to standardize. For these reasons, several attempts have been made to develop tools that allow for a more systematic bleeding risk assessment. Several scores for predicting bleeding risk have been published for patients with AF or VTE [14–21]. All of these scores have categorized patients into low, intermediate, or high bleeding risk groups but with significant differences across studies. Furthermore, few studies validating these bleeding risk scores (BRSs) and their performance in clinical practice have been conducted some of them suggesting inadequate predictive ability [19,22]. Additionally, these scores have all focused on MB events, but none has evaluated the occurrence of other bleeding events that may not be defined as major but are still clinically relevant, either because they result in an increased use of medical resources or because they cause inconvenience, discomfort, or temporary disability.

We aimed to evaluate the clinical performance, risk stratification agreement, and ability to predict MB and clinically relevant non-major bleeding (CRNMB) events of five validated BRSs in a group of patients on warfarin therapy for different indications.

Methods

Study design and patient population

The study was conducted at the Anticoagulation Clinic of the London Health Sciences Centre, University Hospital in London, Ontario, Canada, which primarily monitors patients with cardiac indications for anticoagulation. All patients referred to the clinic have clinical information routinely and prospectively collected at the first clinic visit—including thromboembolic and bleeding risk factors—using standardized forms. We conducted an ambispective cohort study of all consecutive new patients referred to the clinic for warfarin anticoagulation management between September 2008 and February 2011. Patients were included if they had been initiated and/or maintained on warfarin therapy and monitored through the clinic. The study was approved by the Office of Research Ethics at the University of Western Ontario.

Patient demographics, indications for anticoagulation, alcohol and smoking history, laboratory measurements, comorbidities, concomitant medications, potential bleeding risk factors, and BRSs were collected at the first clinic visit using a standardized form. Renal impairment was defined as an estimated creatinine clearance < 30 mL min^{-1}. Outcome events that occurred during the follow-up period were identified from clinic charts, hospital charts, clinic database, and emergency department encounters. When appropriate, hospital charts were reviewed to obtain pertinent clinical information. Adjudication of bleeding events was done by one author using the criteria described hereafter and independently corroborated by a second author. Both authors were blinded to the patients' BRSs.

Information at the first clinic visit was used to calculate patients' MB risk using the following BRSs: modified Outpatient Bleeding Risk Index (mOBRI) [14], Contemporary Bleeding Risk Model (CBRM) [21], HEMORR$_2$HAGES (Hepatic or Renal Disease, Ethanol Abuse, Malignancy, Older Age, Reduced Platelet Count or Function, Re-Bleeding, Hypertension, Anemia, Genetic Factors, Excessive Fall Risk and Stroke) [19], HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile International Normalized Ratio, Elderly, Drugs/Alcohol) [23] and ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) [18]. For each BRS, patients were categorized as being at low, moderate, or high risk for MB. The mOBRI has been tested and validated in populations with mixed indications [14,23], the CBRM was developed in elderly patients, and HAS-BLED and ATRIA were developed specifically in an AF populations. The HEMORR$_2$HAGES score was developed for elderly patients with AF. A description of the bleeding risk tools and the variables included to predict MB is found in Supporting Information Table S1.

Study objectives and clinical outcomes

The objectives of this study were (i) to determine the agreement between the BRS in their stratification of patients into low, moderate, and high bleeding risk categories and (ii) to evaluate the ability of each tool to predict bleeding events. The main clinical outcomes of the study were (i) the occurrence of an MB event defined according to the International Society on Thrombosis and Haemostasis [24] (including fatal bleeding and/or symptomatic bleeding in a critical area or organ and/or bleeding causing a fall in hemoglobin level ≥ 20 g L^{-1} or leading to transfusion of ≥ 2 units of whole blood or red blood cells) and (ii) the occurrence of either an MB or a CRNMB event, the latter defined as those bleeding events not meeting the criteria for MB but associated with medical intervention, unscheduled contact with a physician, temporary cessation of drug therapy, or any other discomfort such as pain or impairment of activities of daily life.

Statistical analysis

Due to the ambispective nature of the study, we conducted a post-hoc power analysis to determine the appropriateness of our sample size to independently evaluate

each BRS as a single covariate using Cox regression. We estimated that a sample size of 321 patients achieved at least 83% power to detect a hazard ratio of 3 at the 0.05 level of significance level adjusted for an anticipated event rate of 3%. The sample is not powered to detect superiority of any model over the others.

Categorical data were compared between groups using χ^2 or Fisher's exact tests as appropriate. Continuous data were compared using Student's *t*-tests or Mann-Whitney *U* tests as appropriate. The incidence of MB and CRNMB was calculated as the number of events per 100 patient-years of follow-up, and 95% confidence intervals (CIs) were calculated using a mid-*P* exact test. Agreement between the bleeding risk tools in stratifying patients into low, moderate, and high bleeding risk categories was quantified using Kendall's tau-b coefficient. The discriminatory ability for both MB and MB plus CRNMB events was calculated for each tool using *c*-statistics [25]. Survival analysis was done according to the method of Kaplan and Meier [26]. Hazard ratios (HRs) and 95% CIs for bleeding risk categories for each tool were estimated with Cox regression analysis using block entry with each score entered as an independent covariate. Exploratory analyses to evaluate adjusted HRs were conducted through stepwise Cox regression. The observation period for each patient started at the first clinic appointment or on the day of warfarin initiation if warfarin was started after the first clinic appointment. Patients were followed until the occurrence of the first MB or CRNMB event and censored at the time of warfarin discontinuation, last clinic contact, death, or end of the study period. For all analyses, P values < 0.05 were considered as statistically significant. Analyses were done using Excel 2007 (Microsoft Corporation, Redmond, WA), OpenEpi version 3.01 (www.openepi.com), and SPSS 20.0 (IBM Corporation, Armonk, NY).

Results

Patient characteristics

Between September 2008 and February 2011, 321 patients started warfarin therapy management at the clinic and were included in the analysis. Baseline characteristics are summarized in Table 1. The cohort was constituted primarily by elderly patients (mean age 69 years), and 57% were males. The most common indication for anticoagulation was AF (74%), and for these patients, the average $CHADS_2$ (Congestive heart failure, Hypertension, Age 75 years, Diabetes mellitus, Stroke) score was 2.6 (SD 1.3). Of the 321 patients, 180 (56%) were warfarin naïve at the time of their first clinic visit. The median length of observation was 319 days (range 20–904). In total, there were 319.3 and 307.3 patient-years of observation when censored at MB event or the composite of MB and CRNMB event, respectively.

Table 1 Baseline patient characteristics

Characteristic	(n = 321)
Demographics	
Mean age (yrs) (SD)	69.2 (13.4)
Male gender (%)	57.0
Mean body mass index (kg per m^2) (SD)	28.8 (5.97)
Previously on warfarin (%)	44.0
Indication for anticoagulation (%)	
Atrial fibrillation/flutter	74.0
Cardioembolic stroke	10.5
Venous thromboembolism	2.5
Prosthetic valve replacement	10.8
LV thrombus	3.2
Heart failure/cardiomyopathy	1.3
Medical conditions (%)	
Atrial fibrillation	78.4
History of myocardial Infarction	21.0
Coronary artery disease	33.0
Previous percutaneous intervention	17.1
Uncontrolled hypertension (SBP > 160 mm Hg)	3.8
Heart failure/cardiomyopathy	31.4
Stroke/transient ischemic attack	39.7
History of gastrointestinal bleed	11.2
History of major bleed	2.9
Hepatic dysfunction	0.3
Renal dysfunction	11.8
Diabetes mellitus	27.1
Active malignancy	5.4
Current smoker	10.2
Concomitant medications	
Antiplatelets (%)	47.7
Triple therapy (%)	3.1
NSAIDs (%)	5.3
Cyclooxygenase inhibitors (%)	0.9
Selective serotonin reuptake inhibitors (%)	8.1
Statin (%)	56.1
Amiodarone (%)	3.4
Corticosteroids (%)	1.9
Proton pump inhibitors (%)	28.7
Number of medications per day, mean (SD)	8 (3.5)
Number of doses per day, mean (SD)	10 (4.9)

SD, standard deviation; LV, left ventricular; NSAIDs, nonsteroidal anti-inflammatory drugs.

Major and clinically relevant non-MB events

During the observation period, 12 MB events occurred, corresponding to an incidence of 3.8 major bleeds per 100 patient-years (95% CI 2.0–6.4) (Table 2). The description of the patients experiencing an MB is shown in Supporting Information Table S2. The average ± SD age was 71.5 ± 14, and five (41.7%) were male. In eight patients (58.3%), the indication for anticoagulation was AF, and the other five patients had prosthetic mechanical heart valves. The average ± SD $CHADS_2$ score in patients with AF was 3.2 ± 1.3. The mean ± SD INR at the time of event was 5.4 ± 4.3. Warfarin therapy was continued in 6 (50%) of the patients experiencing an MB event.

There were 26 CRNMB events during follow-up, corresponding to an incidence of 8.1 clinically relevant non-

Table 2 Incidence rate of major and clinically relevant nonmajor bleeding events according to bleeding risk categories

	Risk category					
	Low		Intermediate		High	
Bleeding risk score	Events per 100 patient-years [95% CI]					
Modified Outpatient Bleeding Risk Index						
MB	6.98	[1.78–18.99]	2.63	[1.07–5.47]	6.15	[1.56–16.73]
MB + CRNMB	9.34	[2.97–22.54]	11.97	[7.98–17.28]	14.68	[6.42–29.03]
Contemporary Bleeding Risk Model						
MB	1.76	[0.56–4.26]	6.62	[2.68–13.77]	79.00	[13.41–264.3]
MB + CRNMB	9.62	[6.11–14.45]	16.12	[9.18–26.42]	79.00	[13.41–264.3]
$HEMORR_2HAGES$						
MB	1.32	[0.23–4.37]	3.71	[1.36–8.23]	14.68	[5.37–32.5]
MB + CRNMB	8.20	[4.44–13.94]	14.06	[8.6–21.8]	20.94	[9.17–41.46]
HAS-BLED						
MB	0.00	NE	2.60	[0.95–5.76]	7.38	[3.23–14.61]
MB + CRNMB	9.87	[2.51–26.86]	9.07	[5.46–14.23]	18.91	[11.38–29.66]
ATRIA						
MB	2.36	[1.03–4.67]	NE	NE	21.22	[7.76–46.96]
MB + CRNMB	10.18	[6.95–14.44]	NE	NE	34.62	[16.08–65.76]

NE, not estimable; MB, major bleeding; CRNMB, clinically relevant non-major bleeding; $HEMORR_2HAGES$, Hepatic or Renal Disease, Ethanol Abuse, Malignancy, Older Age, Reduced Platelet Count or Function, Re-Bleeding, Hypertension, Anemia, Genetic Factors, Excessive Fall Risk, and Stroke; ATRIA, Anticoagulation and Risk Factors in Atrial Fibrillation; HAS-BLED, Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile International Normalized Ratio, Elderly, Drugs/Alcohol.

major bleeds per 100 patient-years (95% CI 4.8–10.3). When MB and CRNMB events were combined, the incidence of any bleeding event was 11.9 per 100 patient-years (95% CI 8.6–16.4). One patient experienced an MB and a CRNMB and was censored at the time of the first event.

Clinical performance of BRSs

Comparison of the bleeding risk stratification by each score revealed variable classification of patients into the three bleeding risk categories, and it is shown along with the corresponding number of bleeding events in Table 3. The proportion of patients classified as low, moderate, and high risk of MB ranged from 10.3% to 91.9%, 29.0% to 69.8%, and 0.9% to 29.6%, respectively. The agreement between risk scores for classifying patients into the same risk categories was low to moderate as assessed by Kendall's tau-b coefficients: the coefficients for agreement between mOBRI compared with CBRM, $HEMORR_2HAGES$, HAS-BLED, and ATRIA were 0.30, 0.36, 0.41, and 0.25, respectively; for CBRM vs. $HEMORR_2HAGES$, HAS-BLED, and ATRIA, the coefficients were 0.39, 0.34, and 0.22, respectively; for $HEMORR_2HAGES$ vs. HAS-BLED and ATRIA, the coefficients were 0.54 and 0.36, respectively, and for HAS-BLED vs. ATRIA, the coefficient was 0.26.

The cumulative incidence of MB in patients classified as low, moderate, or high risk ranged from 0 to 9.8%, 2.5% to 6.5%, and 6.7% to 66.7%, respectively. In general, the high bleeding risk category had the highest incidence of MB events. The *c*-statistics for predicting MB events ranged from 0.606 to 0.735. The scores had even less discriminatory ability to predict MB plus CRNMB events, with *c*-statistics ranging from 0.549 to 0.613. Unadjusted HRs for MB and the composite of major plus CRNMB according to risk category are shown in Table 4. The analysis showed that the mOBRI was unable to predict MB or MB plus CRNMB. In the case of the HAS-BLED score, we were unable to estimate the HR for MB due to the fact that only about 10% of all patients were included in the low-risk category in which there were no MB. For patients classified in the high-risk group, the $HEMORR_2HAGES$, CBRM, and ATRIA scores reported high HRs for MB with highly significant *P*-values, whereas for patient in the moderate-risk category, only the CBRM resulted in an increased HR that was statistically significant. We did not have any patients classified in the moderate-risk category according to the ATRIA score. The analysis of the combined outcome of major plus CRNMB showed that in the patients categorized in the high-risk group, only the CBRM and ATRIA scores reported a statistically significant HR, whereas the $HEMORR_2HAGES$ score achieved marginal significance and the HAS-BLED score did not. For those patients classified in the moderate-risk category, no score demonstrated a statistically significant increase in the HRs of major plus CRNMB, although a trend was found for the CBRM. Exploratory analyses using adjusted HRs for additional potential predictors did not show any change in the results (data not shown).

Table 3 Risk categorization and predictive ability of bleeding risk scores

Bleeding risk score	Bleeding risk categories (n = 321)			
	Low	Moderate	High	c-Statistic (95% CI)
Outpatient Bleeding Risk Index				
Individuals in risk category, n (%)	52 (16.2)	224 (69.8)	45 (14.0)	–
MB, n (%)	3 (5.8)	6 (2.7)	3 (6.7)	0.606 (0.435–0.777)
MB + CRNMB, n (%)	4 (7.7)	27 (12.1)	7 (15.6)	0.549 (0.452–0.645)
Contemporary Bleeding Risk Model				
Individuals in risk category, n (%)	225 (70.1)	93 (29.0)	3 (0.9)	–
MB, n (%)	4 (1.8)	6 (6.5)	2 (66.7)	0.714 (0.548–0.879)
MB + CRNMB, n (%)	21 (9.3)	15 (16.1)	2 (66.7)	0.591 (0.489–0.692)
$HEMORR_2HAGES$				
Individuals in risk category, n (%)	157 (48.9)	132 (41.1)	32 (10.0)	–
MB, n (%)	2 (1.3)	5 (3.8)	5 (15.6)	0.735 (0.583–0.886)
MB + CRNMB, n (%)	12 (7.6)	19 (14.4)	7 (21.9)	0.613 (0.517–0.709)
HAS-BLED				
Individuals in risk category, n (%)	33 (10.3)	193 (60.1)	95 (29.6)	–
MB, n (%)	0 (0.0)	5 (2.6)	7 (7.4)	0.672 (0.523–0.820)
MB + CRNMB, n (%)	3 (9.1)	18 (9.3)	17 (17.9)	0.587 (0.487–0.686)
ATRIA				
Individuals in risk category, n (%)	295 (91.9)	0	26 (8.1)	–
MB, n (%)	7 (2.4)	0	5 (19.2%)	0.674 (0.491–0.858)
MB + CRNMB, n (%)	29 (9.8)	0	8 (30.8)	0.576 (0.470–0.682)

CI, confidence interval; MB, major bleeding; CRNMB, clinically relevant non-major bleeding; $HEMORR_2HAGES$, Hepatic or Renal Disease, Ethanol Abuse, Malignancy, Older Age, Reduced Platelet Count or Function, Re-Bleeding, Hypertension, Anemia, Genetic Factors, Excessive Fall Risk, and Stroke; ATRIA, Anticoagulation and Risk Factors in Atrial Fibrillation; HAS-BLED, Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile International Normalized Ratio, Elderly, Drugs/Alcohol.

Table 4 Unadjusted HRs for bleeding events according to bleeding risk scores

Bleeding risk tool	Major bleeding		Major bleeding plus clinically relevant non-major bleeding	
	HR (95% CI)	P value	HR (95% CI)	P value
Outpatient Bleeding Risk Index				
Low	Reference		Reference	
Moderate	0.38 (0.09–1.51)	0.169	1.29 (0.45–3.69)	0.636
High	0.90 (0.18–4.46)	0.895	1.52 (0.44–5.22)	0.503
Contemporary Bleeding Risk Model				
Low	Reference		Reference	
Moderate	3.67 (1.045–13.01)	0.044	1.79 (0.92–3.48)	0.085
High	39.01 (6.99–217.70)	< 0.001	8.71 (2.02–37.52)	0.004
$HEMORR_2HAGES$				
Low	Reference		Reference	
Moderate	2.77 (0.54–14.28)	0.224	1.80 (0.88–3.72)	0.110
High	10.94 (2.12–56.42)	0.004	2.54 (1.00–6.46)	0.050
HAS-BLED*				
Low	NE	NE	Reference	
Moderate	NE	NE	0.97 (0.29–3.29)	0.959
High	NE	NE	1.91 (0.56–6.52)	0.302
ATRIA†				
Low	Reference		Reference	
Moderate	NE	NE	NE	NE
High	9.09 (2.88–28.68)	< 0.001	3.52 (1.61–7.69)	0.002

NE, not estimable; HR, hazard ratio; CI, confidence interval; $HEMORR_2HAGES$, Hepatic or Renal Disease, Ethanol Abuse, Malignancy, Older Age, Reduced Platelet Count or Function, Re-Bleeding, Hypertension, Anemia, Genetic Factors, Excessive Fall Risk, and Stroke; ATRIA, Anticoagulation and Risk Factors in Atrial Fibrillation; HAS-BLED, Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile International Normalized Ratio, Elderly, Drugs/Alcohol. *There were no major bleeding events in the low-risk category. †No patients were classified in the moderate-risk category.

Discussion

In the present study, we found a moderate correlation between the tested BRS as the scores often classified the same patients into different risk categories. A previous study that assessed the agreement between four scores including the mOBRI, the schemes published by Kearon *et al.* [16] and by Kuijer *et al.* [15], and $HEMORR_2$HAGES reported similar results [19]. A more recent comparison of bleeding risk tools (HAS-BLED, mOBRI, CBRM, Kuijer *et al.* [15], and $HEMORR_2$HAGES) also demonstrated variable classification of patients into various bleeding risk categories [20]. The discrepant stratification of bleeding risk could potentially be explained by methodological or population differences between studies.

In our study, we also found that the BRSs performed poorly for predicting MB events and were generally unable to predict a composite of major plus CRNMB events. Of the five evaluated scores, we found that the mOBRI [14] had no predictive ability for MB or the combined outcome, and we believe that this score should not be used in clinical practice. The HAS-BLED [23] score was the most conservative, classifying only 10.3% of patients in the low-risk category, and having the highest proportion of patients classified as high risk (29.6%). However, this score failed to achieve an acceptable discriminatory power for MB or major plus CRNMB (*c*-statistic 0.672 and 0.587, respectively). In general, it is accepted that a *c*-statistic > 0.7 has acceptable discrimination and a value > 0.8 has excellent discrimination [27]. In comparison, the CBRM [21] only classified 1% patients as high bleeding risk, and among those, 66.7% experienced an MB event. Therefore, this score achieved a better predictive capacity for MB but not for the combined MB plus CRNMB. The $HEMORR_2$HAGES score displayed slightly better discriminatory power for both MB and MB plus CRNMB (*c*-statistics of 0.735 and 0.613, respectively). The ATRIA score was able to predict MB and major plus CRNMB for patients classified as high risk, but this should be interpreted with caution since no patient was classified in the intermediate-risk group. Furthermore, when analyzed by *c*-statistics, it did not perform appropriately. Three previous studies suggested the HAS-BLED score outperforms other bleeding risk tools in predicting MB events [20,23,28]. Lip *et al.* evaluated the predictive value of several bleeding risk tools, including HAS-BLED, $HEMORR_2$HAGES, mOBRI, and the CBRM, using data from the SPORTIF (Stroke Prevention using ORal Thrombin Inhibitor in atrial Fibrillation) III and IV clinical trials [20]. In their analysis, the HAS-BLED score exhibited a marginally better predictive ability compared with the other scores based on comparative *c*-statistics. The HAS-BLED scheme had a *c*-statistic of 0.66, which is almost identical to the predictive ability exhibited in our study. In the initial validation of the HAS-BLED score, it had greater predictive ability for bleeding events (*c*-statistic = 0.72) and outperformed $HEMORR_2$HAGES (*c*-statistic = 0.66) [23]. A recent comparison of HAS-BLED and ATRIA concluded that the former had better performance when analyzed as a dichotomous score (low-moderate vs. high risk) but not as a continuous variable. In contrast, in the present study, the HAS-BLED score did not outperform other clinical prediction tools. Furthermore, the overlap of the *c*-statistic CIs for each score and the lack of accepted methods to compare multiple *c*-statistics make it difficult to evaluate the significance of a slightly greater *c*-statistic; therefore, we cannot conclude that one score is superior in predictive ability. Finally, for all five scores, the 95% CI for the *c*-statistics either cross 0.5 or are very close to it, suggesting that the these scores have a discriminatory power similar to or just slightly better than what would have been expected by chance alone [29].

Our findings are consistent with a recent systematic review and performance analysis of clinical prediction rules for MB risk [30]. The authors concluded that none of the risk scores exhibited sufficient predictive accuracy or had sufficient validation to be recommended in routine clinical practice. At least two recently published studies concluded that the clinical performance of BRS to predict MB events is limited, and in one of them, the authors found that the scores performed no better than clinical gestalt [31,32]. It is possible that a single clinical prediction tool may not be capable of capturing the numerous variables that are associated with increased bleeding risk. However, the most recent versions of the Canadian and European AF guidelines have suggested the use of the HAS-BLED score for bleeding risk assessment in these patients [33–36], but based on our results and those of other authors, we believe that no individual risk scoring system has sufficient reliability to merit recommendation for routine clinical use.

Our study has several limitations. First, this was an ambispective study with all the caveats associated with the retrospective portion of such design. However, all patients had clinical information prospectively collected at the time of their initial assessment using standardized forms. Also, since the occurrence of bleeding events is routinely investigated by the pharmacists during routine monitoring phone calls for warfarin adjustment, we believe that the chance of missing relevant bleeding events during the follow-up period was minimal. Second, our study population is relatively small; however, a power analysis suggested that the sample size was appropriate to evaluate the scores using Cox regression, although we cannot completely rule out the possibility that the relatively low event rate might have influenced some of the observed variability in the results. Additionally, we had a relatively short follow-up, and therefore the occurrence of later events might have been missed. However, our follow-up is similar to that of other studies. It is always

possible that the bleeding risk varies with time, and it has been suggested that it might be higher during warfarin initiation. However, our study included 56% of Warfarin-naive patients, and thus we believe that the bleeding estimates reflect the overall population. Subgroup analyses did not show any major difference between naive patients and those who were not, but these are to be taken with caution given the sample size. Finally, our study reflects the experience of a single academic center and might differ from other settings. Finally, an important contribution of our study is that, to the best of our knowledge, it is the first to evaluate the performance of BRS to predict CRNMB. Our findings suggest that neither of the tested scores performs satisfactorily, although it must be considered that these scores were not originally developed to predict CRNMB. Further studies are needed in this regard.

In conclusion, in our experience, the BRSs evaluated herein have at best a moderate agreement in stratification of bleeding risk and a suboptimal ability for predicting MB or a combination of MB and CRNMB. Therefore, although based on our results we cannot recommend their routine use in clinical practice, they might be helpful to guide clinical assessments or follow-up strategies. It should be remembered that all scores provide only a general guidance on how to evaluate a patient's bleeding risk but should not be a substitute for sound clinical judgment and continued clinical surveillance. Additional studies are needed specifically focused on further refining the previously published BRS, identifying additional clinically relevant variables, evaluating their clinical impact and developing methods to facilitate clinical decision making.

Addendum

A. Lazo-Langner and N. Crown designed the study. S. Burgess, G. Dresser, R. B. Kim, and A. Lazo-Langner collected data. A. Lazo-Langner and M. Louzada analyzed data. S. Burgess, N. Crown, M. L. Louzada, G. Dresser, R. B. Kim, and A. Lazo-Langner wrote the manuscript. All authors agreed to the final version.

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Disclosure of Conflict of Interest

A. Lazo-Langner has received honoraria from Pfizer and Leo Pharma. All other authors declare no competing interests. This study was not funded.

Supporting Information

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

Table S1. Components and calculation of bleeding risk scores

Table S2. Characteristics of patients experiencing major bleeding events

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