



# Evaluation of the HAS-BLED, ATRIA, and ORBIT Bleeding Risk Scores in Patients with Atrial Fibrillation Taking Warfarin

Keitaro Senoo, MD,<sup>a</sup> Marco Proietti, MD,<sup>a</sup> Deirdre A. Lane, PhD,<sup>a</sup> Gregory Y.H. Lip, MD<sup>a,b</sup>

<sup>a</sup>University of Birmingham Institute of Cardiovascular Sciences, City Hospital, Birmingham, United Kingdom; <sup>b</sup>Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark.

## ABSTRACT

**OBJECTIVES:** Various bleeding risk prediction schemes, such as the Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized Ratio, Elderly, Drugs/alcohol (HAS-BLED), Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA), and Outcomes Registry for Better Informed Treatment (ORBIT) scores, have been proposed in patients with atrial fibrillation. We compared the relative predictive values of these bleeding risk scores for clinically relevant bleeding and the relationship of ATRIA and ORBIT scores to the quality of anticoagulation control on warfarin, as reflected by time in therapeutic range.

**METHODS:** We conducted a post hoc ancillary analysis of clinically relevant bleeding and major bleeding events among 2293 patients receiving warfarin therapy in the AMADEUS trial.

**RESULTS:** Only HAS-BLED was significantly predictive for clinically relevant bleeding, and all 3 risk scores were predictive for major bleeding. The predictive performance of HAS-BLED was modest, as reflected by c-indexes of 0.59 ( $P < .001$ ) and 0.65 ( $P < .002$ ) for clinically relevant bleeding and major bleeding, respectively. The HAS-BLED score performed better than the ATRIA ( $P = .002$ ) or ORBIT ( $P = .001$ ) score in predicting any clinically relevant bleeding. Only the HAS-BLED score was significantly associated with the risk for both bleeding outcomes on Cox regression analysis (any clinically relevant bleeding: hazard ratio, 1.85; 95% confidence interval, 1.43-2.40,  $P < .001$ ; major bleeding: hazard ratio, 2.40; 95% confidence interval, 1.28-4.52;  $P = .007$ ). There were strong inverse correlations of ATRIA and ORBIT scores to time in therapeutic range as a continuous variable (low risk ATRIA,  $r = -0.96$ ;  $P = .003$ ; ORBIT,  $r = -0.96$ ;  $P = .003$ ). Improvement in the predictive performance for both ATRIA and ORBIT scores for any clinically relevant bleeding was achieved by adding time in therapeutic range to both scores, with significant differences in c-indexes ( $P = .001$  and  $P = .002$ , respectively), net reclassification improvement, and integrated discriminant improvement (both  $P < .001$ ).

**CONCLUSIONS:** All 3 bleeding risk prediction scores demonstrated modest predictive ability for bleeding outcomes, although the HAS-BLED score performed better than the ATRIA or ORBIT score. Significant improvements in both ATRIA and ORBIT score prediction performances were achieved by adding time in therapeutic range to both scores.

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**KEYWORDS:** Anticoagulation; ATRIA; Bleeding; HAS-BLED; ORBIT; Risk assessment

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Requests for reprints should be addressed to Gregory Y. H Lip, MD, University of Birmingham Institute of Cardiovascular Sciences, City Hospital, Birmingham, UK.

E-mail address: [g.y.h.lip@bham.ac.uk](mailto:g.y.h.lip@bham.ac.uk)

Various bleeding risk scores have been derived in general populations undergoing anticoagulation and validated in patients with atrial fibrillation; for example, the Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized Ratio, Elderly, Drugs/alcohol (HAS-BLED) score<sup>1</sup> and the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) score.<sup>2</sup> More recently, a new bleeding prediction score, the

Outcomes Registry for Better Informed Treatment (ORBIT) score, was developed from a large observational cohort of patients with atrial fibrillation<sup>3</sup> and validated in the Rivaroxaban Once-daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) trial cohort.<sup>4</sup> The ORBIT score was proposed as a simple bedside score, to be used with any oral anticoagulant (vitamin K antagonist, eg, warfarin) or non-vitamin K antagonist oral anticoagulant. In patients taking vitamin K antagonists, both the ATRIA and ORBIT scores do not consider quality of anticoagulation control, as reflected by the time in therapeutic range, whereas the HAS-BLED score includes this within the L criterion (labile international normalized ratio). This is despite time in therapeutic range being strongly correlated to the risk of serious bleeding in patients taking vitamin K antagonists.<sup>5,6</sup>

In this study, we tested the hypothesis that the HAS-BLED score would perform at least as well as the ATRIA and new ORBIT scores in predicting the principal trial safety outcome of any clinically relevant bleeding, in addition to the secondary end point of major bleeding. Second, we hypothesized that the addition of time in therapeutic range to the ATRIA and ORBIT scores would identify additional patients at high risk of clinically relevant bleeding. We tested these hypothesis in a post hoc analysis of warfarin-treated patients from the Evaluating the Use of SR34006 Compared with Warfarin or Acenocoumarol in Patients With Atrial Fibrillation (AMADEUS) trial.<sup>7</sup>

## MATERIALS AND METHODS

The design and results of the AMADEUS trial have been described.<sup>7,8</sup> In brief, this was a multicenter, randomized, open-label noninferiority study with blinded assessment of outcome that compared fixed-dose idraparinix with conventional anticoagulation with dose-adjusted oral vitamin K antagonist for the prevention of thromboembolism in patients with atrial fibrillation and an indication for long-term anticoagulation. Eligible patients had electrocardiogram-documented non-valvular atrial fibrillation and an indication for long-term anticoagulation, based on the presence of at least 1 of the following risk factors: previous ischemic stroke, transient ischemic attack or systemic embolism, hypertension requiring drug treatment, left ventricular dysfunction, age >75 years, or age 65 to 75 years with diabetes mellitus or symptomatic coronary artery disease. Exclusion criteria included the inability to provide consent,

contraindication or other requirement for anticoagulation, calculated creatinine clearance of <10 mL/min, breast-feeding, pregnancy, and recent or anticipated invasive procedures with potential for uncontrolled bleeding. There was blinded assessment of trial outcomes, and for this ancillary analysis, outcomes were analyzed for the warfarin arm of the trial only, because the development of idraparinix has been discontinued and thus less relevant for our clinical practice.

### CLINICAL SIGNIFICANCE

- The HAS-BLED score performed significantly better than the ATRIA and ORBIT scores in predicting clinically relevant bleeding.
- Quality of anticoagulation control (as reflected by time in therapeutic range) was strongly correlated with clinically relevant bleeding events in patients assessed by both ATRIA and ORBIT scores (which do not consider time in therapeutic range).
- Improvements in both ATRIA and ORBIT score prediction performances were achieved by adding time in therapeutic range to both scores.

### Assessment of Bleeding Risk Scores

The acronym HAS-BLED represents each of the bleeding risk factors and assigns 1 point for the presence of each of the following bleeding risk factors: Hypertension (uncontrolled systolic blood pressure >160 mm Hg), Abnormal renal and/or liver function, previous Stroke, Bleeding history or predisposition, Labile international normalized ratio (applies only to a vitamin K antagonist user, otherwise not applicable for a non-vitamin K antagonist user), Elderly (age  $\geq 65$  years), and concomitant

Drugs and/or alcohol excess. In the present analysis, the variable labile international normalized ratio was defined for a time in therapeutic range <60%. For this study, we used each patient's first 5 international normalized ratio measurements after study entry to calculate the time in therapeutic range. A HAS-BLED score of 0 to 2 was categorized as "low risk," and a HAS-BLED  $\geq 3$  was categorized as "high risk."

The ATRIA score was developed from the ATRIA<sup>2</sup> study cohort and calculated using the following: anemia (hemoglobin <13 g/dL in men and <12 g/dL in women) (3 points), severe renal disease (estimated glomerular filtration rate <30 mL/min/1.73 m<sup>2</sup>) (3 points), age  $\geq 75$  years (2 points), prior bleeding, and hypertension. An ATRIA score of 0 to 3 is defined as "low risk," a score of 4 is defined as "intermediate risk," and a score  $\geq 5$  is defined as "high risk."

The ORBIT score was developed from the ORBIT registry<sup>3</sup> and calculated as follows: 1 point each for age >74 years, insufficient kidney function (estimated glomerular filtration rate <60 mL/min/1.73 m<sup>2</sup>), and treatment with any antiplatelet; 2 points were assigned to a positive clinical history for bleeding and the presence of anemia or abnormal hemoglobin (<13 mg/dL for men and <12 mg/dL for women). An ORBIT score of 0 to 2 was "low risk," a score of 3 was "intermediate risk," and a score  $\geq 4$  was "high risk." In the present study, none of the patients had a history of alcohol abuse or major bleeding at study entry, because these were criteria

for exclusion from the AMADEUS trial, and therefore those components were categorized as 0.

## Definitions of End Points

This post hoc analysis of the AMADEUS trial used pooled data from the vitamin K antagonist arm on an intention-to-treat basis. The principal adjudicated safety outcome of the present analysis was any clinically relevant bleeding, which was defined as major bleeding or nonmajor clinically relevant bleeding. The latter was defined as overt bleeding that did not satisfy the criteria for major bleeding but that met predefined criteria and included repetitive epistaxis for more than 5 minutes at least twice in 24 hours, hematuria (spontaneous or lasting >24 hours), hematemesis, and subcutaneous hematomas of more than 25 cm<sup>2</sup> if spontaneous or more than 100 cm<sup>2</sup> if after trauma. Major bleeding was defined as bleeding that was fatal or intracranial or affecting another critical anatomic site, overt bleeding with a decrease of hemoglobin  $\geq 20$  g/L, or bleeding requiring transfusion of 2 or more units of erythrocytes. All suspected outcome events were adjudicated by the original AMADEUS central adjudication committee, who were blinded to treatment assignment.

## Statistical Analysis

All continuous variables were tested for normality with the Shapiro-Wilk test. Variables with normal distribution were expressed as means and standard deviations. Nonparametric variables were expressed as median and interquartile range (IQR). Categorical variables, expressed as counts and percentages, were analyzed by the chi-square test. Bleeding outcomes by each bleeding risk scheme were calculated as the overall rate of adverse events per 100 patient-years.

A Cox regression analysis was performed to investigate the association among 3 bleeding risk schemes and bleeding outcomes, such as any clinically relevant bleeding and major bleeding. Pearson correlations and regression analyses were performed between time in therapeutic range and any clinically relevant bleeding in relation to the ATRIA and ORBIT scores.

Receiver operating characteristic curves were compiled for the 3 risk scores, according to bleeding outcomes, to evaluate their predictive ability using the area under the curve method (a measure of their c-index). Their respective areas under the curve were then compared according with DeLong et al's method.<sup>9</sup> We also tested the predictive ability of the ATRIA and ORBIT scores with and without the addition of time in therapeutic range by comparing areas under the curve and calculating the net reclassification improvement and integrated discrimination improvement using PredicABEL, an R package for the assessment of risk prediction model.<sup>10,11</sup> A 2-sided *P* value <.05 was considered statistically significant. All analyses were performed using SPSS v. 22.0 (IBM, New York, NY), MedCalc v. 15.6 (MedCalc Software, Oostende, Belgium), and R statistic for Windows 3.2.2.

## RESULTS

The AMADEUS study randomized 2293 patients to warfarin (65% were male; median age, 71 years; IQR, 64-77). In total, 251 patients (11%) experienced at least 1 clinically relevant bleeding event, and 39 patients (1.7%) had at least 1 episode of major bleeding. Demographic and clinical characteristics of the AMADEUS population are summarized in **Table 1**. Bleeding event rates in the study population, as stratified by the 3 bleeding scores, are shown in **Figure 1**.

### Predictive Performance of HAS-BLED, ATRIA, and ORBIT

The median HAS-BLED score in the study cohort was 2 (IQR, 1-2), the median ATRIA score was 1 (IQR, 1-3), and the median ORBIT score was 1 (IQR, 0-1). Only HAS-BLED was significantly predictive for clinically relevant bleeding, and all 3 scores were predictive for major bleeding. The predictive performance of HAS-BLED was modest, as reflected by c-indexes of 0.59 (*P* < .001) and 0.65 (*P* < .002), for clinically relevant bleeding and major bleeding, respectively. Corresponding c-indexes for the ATRIA score were 0.50 (*P* = .80, nonsignificant) and 0.61 (*P* = .02), respectively. For the ORBIT score, c-indexes were 0.52 (*P* = .30, nonsignificant) and 0.61 (*P* = .02), respectively (**Figure 2**).

In a Cox regression analysis, a HAS-BLED score  $\geq 3$  was associated with a 1.85-fold greater hazard for any clinically relevant bleeding (*P* < .001) and a 2.4-fold greater hazard for major bleeding (*P* = .007). On a similar Cox regression analysis, an ATRIA score  $\geq 4$  was not significantly associated with any clinically relevant bleeding (*P* = .54) but was associated with a 2.4-fold greater hazard of major bleeding (*P* = .03). An ORBIT score  $\geq 3$  was not significantly associated with any clinically relevant bleeding (*P* = .36) but was associated with a 2.9-fold greater hazard of major bleeding (*P* = .01) (**Table 2**).

### Comparison of Bleeding Scores

The HAS-BLED score performed significantly better than the ATRIA (*P* = .002) or ORBIT (*P* = .001) score in predicting any clinically relevant bleeding, as reflected by comparison of area under the curve analyses (**Table 3**). The areas under the curve for ATRIA vs ORBIT were similar (*P* = .66). For major bleeding, area under the curve differences for the 3 scores did not reach statistical significance.

### Impact of Time in Therapeutic Range on the ORBIT and ATRIA Scores

Any clinically relevant bleeding in relation to tertiles of time to therapeutic range and time to therapeutic range as a continuous variable by ORBIT and ATRIA scores is shown in **Figure 3**.

There was a high absolute event rate for clinically relevant bleeding among patients with poor anticoagulation

**Table 1** Demographic and Clinical Characteristics of Patients Taking Warfarin (n = 2293)

	Overall population (n = 2293)
Age, y (IQR)	71 (64-77)
Male (%)	1501 (65.5)
Body mass index (IQR)	28 (25.3-31.2)
Type of AF (%)	
1. Paroxysmal	813 (35.5)
2. Persistent	214 (9.3)
3. Permanent	1258 (54.9)
Hypertension (%)	1764 (76.9)
Heart failure (%)	543 (23.7)
Diabetes mellitus (%)	450 (19.6)
Coronary artery disease (∧)	718 (31.3)
Stroke/TIA (%)	575 (25.1)
Creatinine clearance mL/min (IQR)	71.4 (55.2-91.7)
Time in therapeutic range (IQR)	58 (45-70)
Use of aspirin (%)	379 (16.5)
Use of NSAID (%)	123 (5.4)
CHA <sub>2</sub> DS <sub>2</sub> -VASc score (IQR)	3 (2-4)
1 (%)	180 (7.8)
2 (%)	481 (21)
3 (%)	567 (24.7)
4 (%)	501 (21.8)
5 (%)	321 (14)
6 (%)	160 (7)
7 (%)	68 (3)
8 (%)	14 (0.6)
9 (%)	1 (0.0)
HAS-BLED score (IQR)	2 (1-2)
Low: <3 (%)	1739 (75.9)
High: ≥3 (%)	553 (24.1)
ATRIA score (IQR)	1 (1-3)
Low: 0-3 (%)	2042 (90.1)
Intermediate: 4 (%)	98 (4.3)
High: ≥5 (%)	127 (5.6)
ORBIT score (IQR)	1 (0-1)
Low: 0-2 (%)	2106 (92.9)
Intermediate: 3 (%)	129 (5.7)
High: ≥4 (%)	32 (1.4)

AF = atrial fibrillation; ATRIA score = Anticoagulation and Risk Factors in Atrial Fibrillation; CHA<sub>2</sub>DS<sub>2</sub>-VASc score = Congestive heart failure, Hypertension, Age ≥75 years (2 points), Diabetes mellitus, previous Stroke/transient ischemic attack/thromboembolism (2 points), Vascular disease, Age 65-74 years, and female gender; HAS-BLED score = Hypertension, Abnormal renal/liver function, Stroke, Bleeding history, Labile international normalized Ratio, Elderly (age ≥65 years), drugs or alcohol concomitant IQR = interquartile range; NSAID = nonsteroidal anti-inflammatory drug; ORBIT = Outcomes Registry for Better Informed Treatment, treatment with antiplatelet; TIA = transient ischemic attack

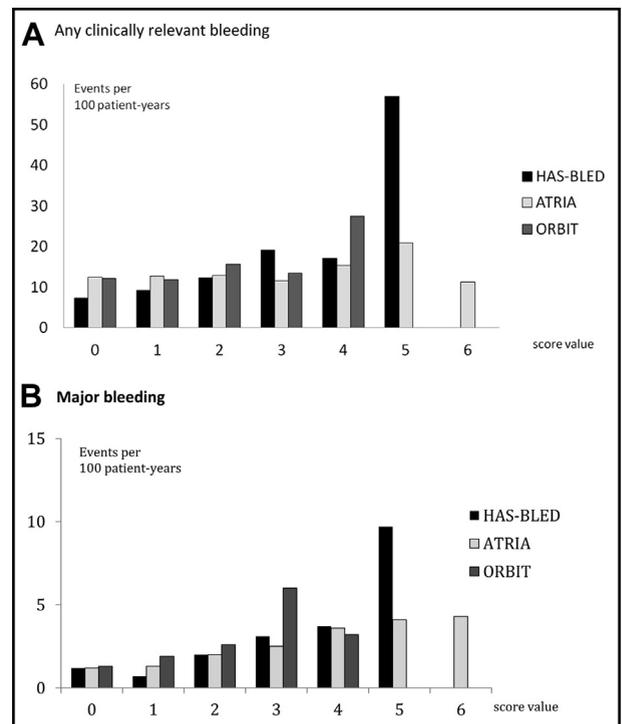
control (time in therapeutic range <50%; ie, >15 per 100 person-years) even among those categorized as low risk using these 2 scores, whereas there was a strong negative correlation to time in therapeutic range as a continuous variable (ATRIA, Pearson  $r = -0.96$ ;  $P = .003$ ; ORBIT,  $r = -0.96$ ;  $P = .003$ ). This correlation was also significant for the ATRIA intermediate/high score group ( $r = -0.85$ ;

$P = .03$ ), with a nonsignificant trend for the ORBIT intermediate/high score group ( $r = -0.77$ ;  $P = .07$ ).

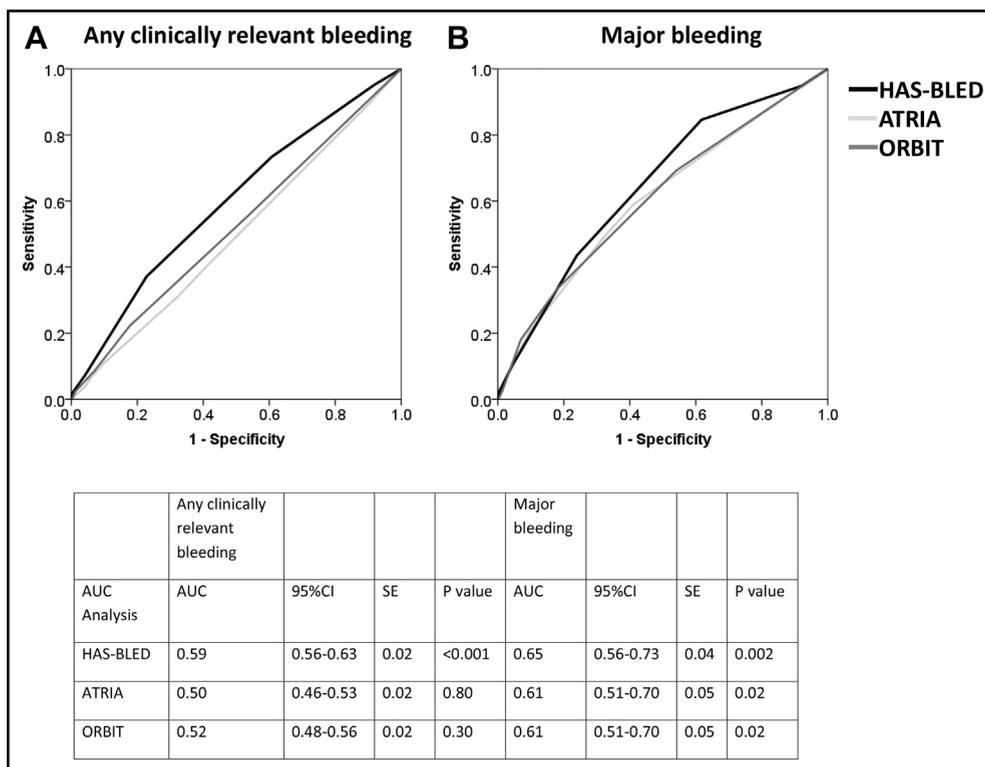
The improvements in prediction performance by adding time in therapeutic range to the ATRIA or ORBIT scores are shown in **Table 4**. For the ATRIA score, adding time in therapeutic range would result in a significant improvement in area under the curve ( $P = .001$ ), with a net reclassification improvement of 0.26 ( $P < .001$ ) and an integrated discriminant improvement of 0.0066 ( $P < .001$ ), compared with the ATRIA score without time in therapeutic range. For the ORBIT score, the area under the curve difference was also significant ( $P = .002$ ), with net reclassification improvement of 0.26 ( $P < .001$ ) and integrated discriminant improvement of 0.0065 ( $P < .001$ ).

**DISCUSSION**

In this study, we compared the ability of the HAS-BLED, ATRIA, and ORBIT scores to predict bleeding events in a clinical trial cohort of patients with atrial fibrillation taking warfarin and examined the relationship of these scores to time in therapeutic range. We show that the HAS-BLED score performed better than the ATRIA and ORBIT



**Figure 1** Incidence rate of bleeding outcomes according to HAS-BLED, ATRIA, and ORBIT scores. (A) Any clinically relevant bleeding. (B) Major bleeding. 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; ORBIT = Outcomes Registry for Better Informed Treatment.



**Figure 2** Area under the curve for bleeding end points with the 3 bleeding risk scores. (A) Any clinically relevant bleeding. (B) Major bleeding. ATRIA = Anticoagulation and Risk Factors in Atrial Fibrillation; AUC = area under the curve; CI = confidence interval; HAS-BLED = Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized Ratio, Elderly, Drugs/alcohol; ORBIT = Outcomes Registry for Better Informed Treatment; SE = standard error.

scores, especially in predicting clinically relevant bleeding events. Second, there was a strong correlation of time in therapeutic range with clinically relevant bleeding events in patients assessed by the ATRIA and ORBIT, even among those categorized as low risk. Third, we show clear improvements in prediction performance by adding time in therapeutic range to both the ATRIA and ORBIT scores.

Despite the increasing use of non-vitamin K antagonist oral anticoagulants, the vitamin K antagonists are still widely used worldwide, and increasing attention has been directed to the importance of good anticoagulation control, as reflected by the time in therapeutic range. The HAS-BLED score

accounts for labile international normalized ratios (the “L” criterion, which is only applicable for a patient taking a vitamin K antagonist) by giving it 1 point, but the ATRIA and ORBIT scores do not recognize the importance of this criterion when calculating risk. This is despite evidence that labile international normalized ratios (whether defined by poor time in therapeutic ranges or other measures indicative of poor anticoagulation control<sup>6,12,13</sup>) are a strong predictor of excess bleeding risk. Indeed, we demonstrate that the risk of any clinically relevant bleeding (and major bleeding) decreases overall with better anticoagulation control. Of note, there was a high absolute event rate for clinically relevant

**Table 2** Cox Regression Analysis of HAS-BLED, ATRIA, and ORBIT Scores for Bleeding Outcomes

	Any Clinically Relevant Bleeding		Major Bleeding	
	HR (95% CI)	P Value	HR (95% CI)	P Value
HAS-BLED high score ( $\geq 3$ )	1.85 (1.43-2.40)	<.001	2.40 (1.28-4.52)	.007
ATRIA Intermediate/high score ( $\geq 4$ )	1.13 (0.76-1.69)	.54	2.40 (1.10-5.22)	.03
ORBIT Intermediate/high score ( $\geq 3$ )	1.23 (0.79-1.93)	.36	2.93 (1.29-6.64)	.01

ATRIA = Anticoagulation and Risk Factors in Atrial Fibrillation; CI = confidence interval; HAS-BLED = Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized Ratio, Elderly, Drugs/alcohol; HR = hazard ratio; ORBIT = Outcomes Registry for Better Informed Treatment.

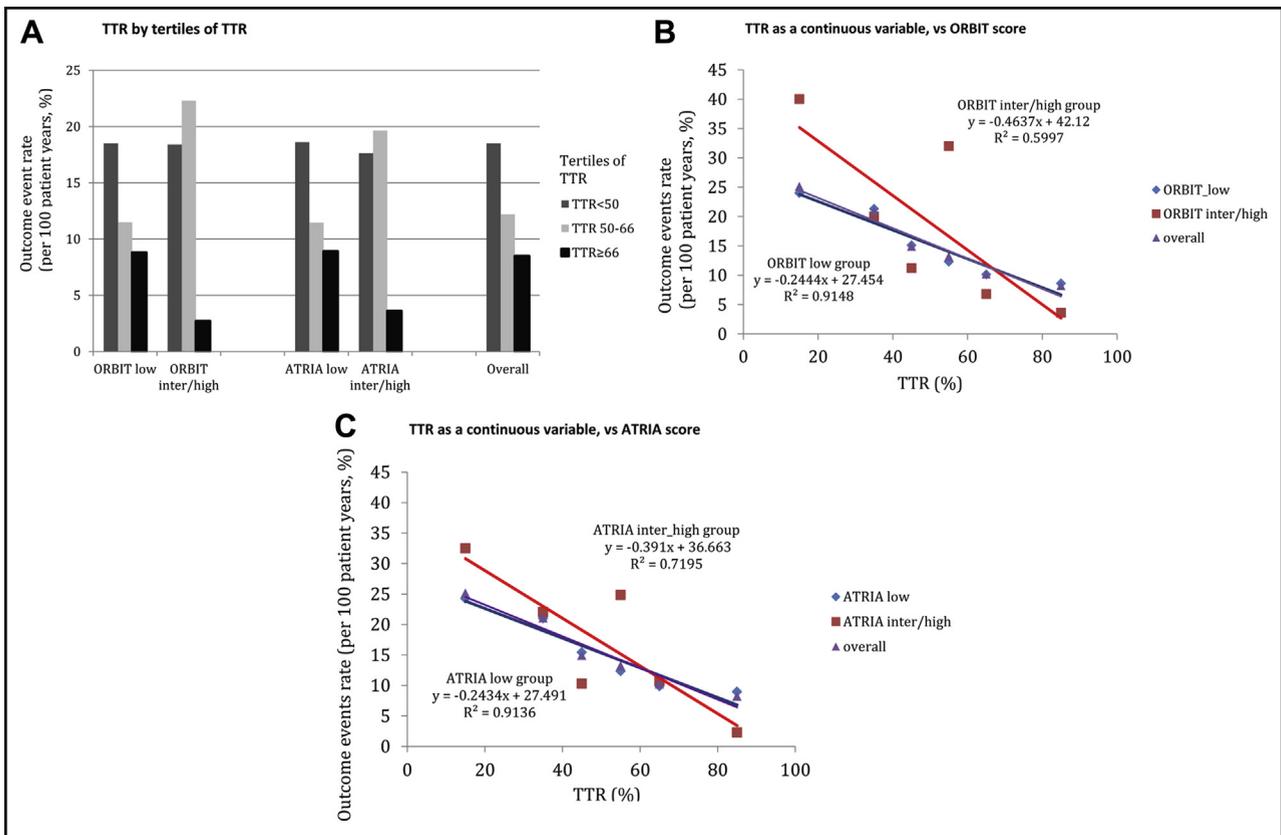
**Table 3** Comparison of Areas Under the Curve for HAS-BLED, ATRIA, and ORBIT scores

Comparison	Any Clinically Relevant Bleeding			Major Bleeding		
	AUC Difference (95% CI)	Z Score	P Value	AUC Difference (95% CI)	Z Score	P Value
HAS-BLED vs ATRIA	0.09 (0.03-0.15)	3.11	.002	0.04 (-0.06 to 0.14)	0.80	.42
HAS-BLED vs ORBIT	0.07 (0.03-0.12)	3.39	.001	0.04 (-0.06 to 0.14)	0.74	.46
ATRIA vs ORBIT	0.02 (-0.05 to 0.08)	0.44	.66	0.002 (-0.05 to 0.05)	0.07	.94

ATRIA = Anticoagulation and Risk Factors in Atrial Fibrillation; AUC = area under the curve; CI = confidence interval; HAS-BLED = Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized Ratio, Elderly, Drugs/alcohol; ORBIT = Outcomes Registry for Better Informed Treatment.

bleeding among the patients with poor anticoagulation control (time in therapeutic range <50%; >15 per 100 person-years) even among those categorized as low risk using the ATRIA and ORBIT scores, as well as a strong negative correlation to time in therapeutic range when analyzed as a continuous variable with these 2 bleeding scores. Significant improvements in score predictive performance were gained by adding time in therapeutic range to both ATRIA and ORBIT scores for clinically relevant bleeding, as reflected by a significant difference in area under the curve, net reclassification

improvement, and integrated discriminant improvement. Thus, both these scores may perform suboptimally in identifying serious bleeding risk in a patient taking a vitamin K antagonist, unless they are recalibrated taking labile international normalized ratios (or time in therapeutic ranges) into consideration. The HAS-BLED score already considers labile international normalized ratio as one of its criteria, which is applicable only for a vitamin K antagonist user (whereas the L criterion is not applicable if a non-vitamin K antagonist oral anticoagulant is used).



**Figure 3** Any clinically relevant bleeding in relation to tertiles of time to therapeutic range and time in therapeutic range as a continuous variable, by ORBIT and ATRIA scores. (A) Time in therapeutic range by tertiles of time in therapeutic range. (B) Time in therapeutic range as a continuous variable vs ORBIT score. (C) Time in therapeutic range as a continuous variable vs ATRIA score. ATRIA = Anticoagulation and Risk Factors in Atrial Fibrillation; ORBIT = Outcomes Registry for Better Informed Treatment; TTR = time in therapeutic range.

**Table 4** Prediction Performance by Adding Time in Therapeutic Range to the ATRIA and ORBIT Scores

ATRIA + TTR vs ATRIA	Any Clinically Relevant Bleeding		Major Bleeding		ORBIT + TTR vs ORBIT	Any Clinically Relevant Bleeding		Major Bleeding	
	P Value	P Value	P Value	P Value		P Value	P Value	P Value	
AUC difference	0.064	.001	0.039	.251	0.054	.002	0.036	.282	
NRI	0.260	<.001	0.348	.02	0.260	<.001	0.348	.02	
IDI	0.0066	<.001	0.002	.065	0.0065	<.001	0.0019	.058	

ATRIA = Anticoagulation and Risk Factors in Atrial Fibrillation; AUC = area under the curve; IDI = integrated discriminant improvement; NRI = net reclassification improvement; ORBIT = Outcomes Registry for Better Informed Treatment; TTR = time to therapeutic range.

Since its original description in the Euro Heart survey, the HAS-BLED score has been validated in both large real-world and clinical trial populations, and recently reviewed in a comprehensive European consensus document.<sup>14</sup> Prior direct comparisons with other bleeding prediction scores, such as Hepatic or Renal Disease, Ethanol Abuse, Malignancy, Older Age, Reduced Platelet Count or Function, Re-Bleeding, Hypertension, Anaemia, Genetic Factors, Excessive Fall Risk and Stroke (HEMORR<sub>2</sub>HAGES) and ATRIA, have shown that the HAS-BLED score is as good as—and possibly better—than other scores in the evaluation of bleeding risk.<sup>8,15</sup> The more recently proposed ORBIT score was derived from a large industry-sponsored registry and validated in the ROCKET-AF trial cohort, with the claim to be simple and applicable to all anticoagulants, whether vitamin K antagonist or non-vitamin K antagonist oral anticoagulant.<sup>3</sup>

As shown in the present study, all 3 bleeding scores showed modest discriminatory capacity for bleeding outcomes, as reflected by c-indexes <0.70, although the HAS-BLED was the only score predictive of both clinically relevant and major bleeding. For major bleeding events, all 3 scores demonstrated similar predictive ability, but with c-indexes <0.70. These c-indexes (~0.6) are perhaps typical of clinical risk scores based on clinical features, including those used for stroke risk prediction, such as the CHADS<sub>2</sub> and Congestive heart failure, Hypertension, Age ≥ 75 years (2 points), Diabetes mellitus, previous Stroke/transient ischemic attack/thromboembolism (2 points), Vascular disease, Age 65-74 years, and female gender (CHA<sub>2</sub>DS<sub>2</sub>-VASC) scores. Rather than undue focus on statistical significance in predicting the high-risk patients who develop an event, the clinical applicability of bleeding risk scores requires attention to the reversible risk factors for bleeding,<sup>16</sup> especially because both stroke and bleeding risks are closely associated.

For example, the HAS-BLED score is used to “flag up” the patient potentially at high risk of bleeding, who may require more careful review and follow-up, and to direct attention to the potentially reversible bleeding risk factors, such as uncontrolled hypertension (the H criterion), labile international normalized ratios (the L criterion), and concomitant drugs (aspirin, nonsteroidal anti-inflammatory drugs) or excess alcohol (the D criterion), that the responsible clinician can address. Indeed, this is the approach

recommended in current guidelines.<sup>12,17</sup> Of note, the ORBIT score does not include uncontrolled hypertension, labile international normalized ratios, alcohol excess, or concomitant nonsteroidal anti-inflammatory drugs within its criteria.<sup>16</sup>

A high HAS-BLED score is not a reason to withhold oral anticoagulants, because such patients derive an even greater net clinical benefit when balancing stroke prevention against the potential for increased serious bleeding,<sup>18,19</sup> an approach also recommended in guidelines.<sup>12,17</sup> The HAS-BLED score also has been validated for predicting bleeding in patients receiving no antithrombotic therapy or aspirin, as well as taking an oral anticoagulant, whether vitamin K antagonist or non-vitamin K antagonist types of anticoagulation, and in patients with and without atrial fibrillation. Thus, the HAS-BLED score would be applicable throughout the patient pathway, which is an important consideration given that risk assessment is not a static process and the patient's risk evolves over time. The ORBIT score has been validated only in anticoagulated patients.

## Study Limitations

These results are based on a post hoc analysis of the AMADEUS trial and should be interpreted as hypothesis generating. The AMADEUS trial population was perhaps at relatively low risk for bleeding events when compared with patients with atrial fibrillation in clinical practice, because patients with a history of major bleeding events were excluded from this trial.

## CONCLUSIONS

The HAS-BLED, ATRIA, and ORBIT bleeding risk scores all demonstrated modest performance in predicting bleeding outcomes, although the HAS-BLED score performed significantly better than the ORBIT and ATRIA scores in predicting clinically relevant bleeding. Time in therapeutic range was strongly correlated with clinically relevant bleeding events in patients assessed by the ATRIA and ORBIT scores, even among those categorized as low risk. Significant improvements in both ATRIA and ORBIT score prediction performances were achieved by considering the quality of anticoagulation control and adding time in therapeutic range to both scores.

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