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Performance of the HEMORR$_2$HAGES, ATRIA, and HAS-BLED Bleeding Risk–Prediction Scores in Patients With Atrial Fibrillation Undergoing Anticoagulation

The AMADEUS (Evaluating the Use of SR34006 Compared to Warfarin or Acenocoumarol in Patients With Atrial Fibrillation) Study

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Objectives The objective of this study was to compare the predictive performance of bleeding risk–estimation tools in a cohort of patients with atrial fibrillation (AF) undergoing anticoagulation.

Background Three bleeding risk–prediction schemes have been derived for and validated in patients with AF: 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). The relative predictive values of these bleeding scores have not previously been compared.

Methods We analyzed the dataset from the AMADEUS (Evaluating the Use of SR34006 Compared to Warfarin or Acenocoumarol in Patients With Atrial Fibrillation) trial, a multicenter, randomized, open-label noninferiority study that compared fixed-dose idraparinux with adjustable-dose oral vitamin K antagonist therapy in patients with AF. The principal safety outcome was any clinically relevant bleeding event, which was a composite of major bleeding plus clinically relevant nonmajor bleeding.

Results The HAS-BLED score performed best in predicting any clinically relevant bleeding, reflected both in net reclassification improvement (10.3% and 13% improvement compared with HEMORR$_2$HAGES and ATRIA, respectively) and receiver-operating characteristic (ROC) analyses (c-indexes: 0.60 vs. 0.55 and 0.50 for HAS-BLED vs. HEMORR$_2$AGES and ATRIA, respectively). Using decision-curve analysis, the HAS-BLED score demonstrated superior performance compared with ATRIA and HEMORR$_2$HAGES at any threshold probability for clinically relevant bleeding. HAS-BLED was the only score that demonstrated a significant predictive performance for intracranial hemorrhage (c-index: 0.75; $p = 0.03$). An ATRIA score >3 was not significantly associated with the risk for any clinically relevant bleeding on Cox regression or on ROC analysis (c-index: 0.50; $p = 0.87$).

Conclusions All 3 tested bleeding risk–prediction scores demonstrated only modest performance in predicting any clinically relevant bleeding, although the HAS-BLED score performed better than the HEMORR$_2$HAGES and ATRIA scores, as reflected by ROC analysis, reclassification analysis, and decision-curve analysis. Only HAS-BLED demonstrated a significant predictive performance for intracranial hemorrhage. Given its simplicity, the HAS-BLED score may be an attractive method for the estimation of oral anticoagulant–related bleeding risk for use in clinical practice, supporting recommendations in international guidelines. (J Am Coll Cardiol 2012;60:861–7) © 2012 by the American College of Cardiology Foundation

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Abbreviations and Acronyms

AF = atrial fibrillation

ATRIA = Anticoagulation and Risk Factors in Atrial Fibrillation

DCA = decision-curve analysis

HAS-BLED = Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile International Normalized Ratio, Elderly, Drugs/Alcohol

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

ROC = receiver-operating characteristic

Although various bleeding risk–prediction tools have been derived in general populations undergoing anticoagulation, only 3 schemes have been initially derived for and validated exclusively in patients with atrial fibrillation (AF): 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) (1); HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile International Normalized Ratio, Elderly, Drugs/Alcohol) (2); and ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) (3).

In the present study, the relative predictive values of these 3 tools used for AF bleeding risk assessment were compared in a post hoc analysis of data from warfarin-treated patients in the AMADEUS (Evaluating the Use of SR34006 Compared to Warfarin or Acenocoumarol in Patients With Atrial Fibrillation) trial. We tested the hypothesis that HAS-BLED would perform at least as well as the (older, more complex) HEMORR$_2$HAGES and new (weighted) ATRIA tools in predicting the principal trial safety outcome of clinically relevant bleeding events. Secondary objectives included testing these schemes for the endpoints of major bleeding only and death.

Patients and Methods

Study population. The study design of AMADEUS has been previously described (4). A detailed description of the study design is provided in the Online Appendix.

Calculation of bleeding risk scores. Bleeding risk scores in each patient were estimated on the basis of the definitions used in their validation cohorts (Online Table 1), with the following limitations: 1) in the absence of relative data, genetic factors associated with an increased risk for bleeding were not used in the calculation of the HEMORR$_2$HAGES score; 2) none of the patients had a history of active malignancy, alcohol abuse, or major bleeding at study entry, as these were criteria for exclusion from the trial; and 3) in the absence of data on prior international normalized ratio (INR) control, we used each patient's first 5 INR measurements following study entry to calculate time in therapeutic range.

Study endpoints. We used data only from the vitamin K antagonist arm and included events that occurred both in the

Table 1 The AMADEUS Patients Randomized to VKA Stratified by Presence or Absence of Bleeding Events During the On-Treatment and Observational Study Period

Characteristic	No Bleeding Events (n = 2,041)	Any Clinically Relevant Bleeding (n = 251)	p Value
Demographics			
Age, yrs	70 ± 9	71 ± 8	0.40
Age ≥75 yrs	737 (36.1)	87 (34.7)	0.68
Age 65 to <75 yrs	705 (34.5)	101 (40.2)	0.08
Male	1,328 (65.1)	173 (68.9)	0.23
Disease history			
Hypertension (diagnosed)	1,575 (77.2)	189 (75.3)	0.53
Uncontrolled hypertension (SBP >160 mm Hg)	273 (13.4)	37 (14.7)	0.56
Diabetes mellitus	394 (19.3)	56 (22.3)	0.27
Previous stroke	270 (13.2)	39 (15.5)	0.33
Previous TIA	229 (11.2)	27 (10.8)	0.92
Coronary artery disease	618 (30.3)	100 (39.8)	0.002
Laboratory analysis			
Left ventricular dysfunction	482 (23.6)	61 (24.3)	0.81
Renal impairment (CrCl <30 ml/min)	6 (0.3)	1 (0.4)	0.55
Liver impairment*	27 (1.3)	4 (1.6)	0.77
Reduced platelet count†	3 (0.1)	3 (1.2)	0.02
Anemia‡	221 (10.9)	29 (11.6)	0.75
Concurrent treatment			
Antiplatelet	365 (17.9)	71 (28.3)	<0.0001
NSAID	277 (13.6)	51 (20.3)	0.005
TTR			
Mean ± SD	58 ± 20	0.53 ± 0.2	<0.0001
Patients with TTR <60%	1,036 (50.8)	159 (63.3)	<0.0001
CHADS$_2$ score§	2.1 ± 1.2	2.1 ± 1.2	0.59
Patients with each score			0.69
0	47 (2.3)	7 (2.8)	
1	740 (36.2)	84 (33.5)	
2	635 (31.1)	81 (32.3)	
3	357 (17.5)	46 (18.3)	
4	199 (9.7)	22 (8.8)	
5	57 (2.8)	11 (4.4)	
6	7 (0.3)	0	
CHA$_2$DS$_2$VASc score‖	3.5 ± 1.5	3.6 ± 1.5	0.12
Patients with each score			0.79
0	0	0	
1	163 (8)	16 (6.4)	
2	435 (21.3)	46 (18.3)	
3	505 (24.7)	62 (24.7)	
4	442 (21.6)	59 (23.5)	
5	281 (13.8)	40 (15.9)	
6	144 (7.1)	16 (6.4)	
7	59 (2.9)	9 (3.6)	
8	12 (0.6)	3 (1.2)	
9	1 (0.1)	0	

Values are mean ± SD or n (%). *Defined as >2-fold increase of alanine aminotransferase and/or aspartate transaminase. †Defined as <75,000 platelets. ‡Defined as hemoglobin <13 g/dl in men and <12 g/dl in women. §CHADS$_2$, congestive heart failure, hypertension, age >75 years, diabetes (1 point for each); stroke (2 points). ‖CHA$_2$DS$_2$VASc, congestive heart failure, hypertension, age ≥75 years, diabetes, stroke, vascular disease, age 65 to <75 years, sex category (female) (1 point each; 2 points for age ≥75 years and previous stroke).

CrCl = creatinine clearance; NSAID = nonsteroidal anti-inflammatory drug; SBP = systolic blood pressure; TIA = transient ischemic attack; TTR = time in therapeutic range; VKA = vitamin K antagonist.

Table 2 AMADEUS Cohort Stratified by the HEMORR$_2$HAGES, HAS-BLED, and ATRIA Schemes

Scheme	All Patients	Clinically Relevant Bleeding	Major Bleeding
HEMORR$_2$HAGES			
0	777 (34.3)	64 (8.2)	8 (1)
1	961 (42.4)	118 (12.3)	17 (1.8)
2	432 (19)	50 (11.6)	9 (2.1)
3	85 (3.7)	13 (15.3)	4 (4.7)
≥4	13 (0.5)	3 (23.1)	1 (7.6)
Risk			
Low (≤1)	1,738 (76.6)	182 (10.5)	25 (1.4)
Intermediate (2–3)	517 (22.8)	63 (12.2)	13 (2.5)
High (>3)	13 (0.5)	3 (23.1)	1 (7.7)
Total	2268	248 (10.9)	39 (1.7)
HAS-BLED			
0	179 (7.8)	12 (6.7)	2 (1.1)
1	689 (30.1)	55 (8)	4 (0.6)
2	871 (38)	92 (10.6)	16 (1.8)
3	451 (19.7)	74(16.4)	13 (2.9)
4	89 (3.9)	13 (14.6)	3 (3.4)
≥5	13 (0.6)	5 (38.5)	1 (7.7)
Risk			
Low (<3)	1,739 (75.9)	159 (9.1)	22 (1.3)
High (≥3)	553 (24.1)	92 (16.6)	17 (3.1)
Total	2,292	251 (11.0)	39 (1.7)
ATRIA			
0	258 (11.4)	30 (11.6)	3 (1.2)
1	1,066 (47)	116 (10.9)	13 (1.2)
2	211 (9.3)	24 (11.4)	4 (1.9)
3	503 (22.2)	50 (9.9)	11 (2.2)
4	102 (4.5)	13 (12.7)	3 (2.9)
5	28 (1.2)	5 (17.9)	1 (3.6)
6	99 (4.3)	10 (10.1)	4 (4)
≥7	1 (0.1)	0 (0)	0 (0)
Risk			
Low (<4)	2,038 (90)	220 (10.8)	31 (1.5)
Intermediate (4)	102 (4.4)	13 (12.7)	3 (2.9)
High (>4)	128 (5.6)	18 (14.1)	5 (3.9)
Total	2,268	248 (10.9)	39 (1.7)

Values are n (%).

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; 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.

randomization/on treatment period and in the observational period, which followed for a follow-up of 429 ± 118 days. The principal safety outcome of the trial was any clinically relevant bleeding event, subclassified as major bleeding and clinically relevant nonmajor bleeding. Definitions of the study endpoints are provided in the Online Appendix.

Statistical analysis. The prognostic value of each score was determined using Cox proportional hazards analysis. C-indexes were calculated for each of the study endpoints. Net reclassification improvement and decision-curve analysis (DCA) were used to quantify the clinical usefulness of the prediction models. Further details on the statistical methods are provided in the Online Appendix.

Results

The AMADEUS study randomized 2,293 patients to the vitamin K antagonist arm (65% men; mean age: 70.2 ± 9.1 years). In total, 251 (11%) patients experienced at least 1 clinically relevant bleeding event. Thirty-nine (1.7%) patients had at least 1 episode of major bleeding. The demographic and clinical characteristics of the AMADEUS population are summarized in Table 1. The bleeding event rates in the study population, stratified by the three bleeding estimation schemas, are summarized in Table 2.

The HEMORR$_2$HAGES bleeding scheme. Median score in the cohort was 1 (interquartile range: 0 to 1). The predictive performance of HEMORR$_2$HAGES for both the study bleeding outcomes was modest, as reflected by c-index of 0.55 and 0.60, for clinically relevant bleeding and major bleeding, respectively (Table 3, Fig. 1). In a Cox regression analysis, a HEMORR$_2$HAGES score >1 was associated with a significantly higher risk of all cause mortality but this score was not associated with bleeding—regardless of whether defined as major or clinically relevant bleeding (Table 4, Online Fig. 1).

The HAS-BLED bleeding scheme. The median HAS-BLED score in the cohort was 2 (interquartile range: 1 to 2). The predictive performance of HAS-BLED for both the study bleeding outcomes was modest, as reflected by c-index of 0.60 and 0.65, for clinically relevant bleeding and major bleeding, respectively (Table 3, Fig. 1). In a Cox regression analysis, a HAS-BLED score >2 was associated with an 85% higher risk for any clinically relevant bleeding and a 2.4-fold higher risk for major bleeding (Table 4, Online Fig. 1). A HAS-BLED score >2 was also associated with 2.9 fold greater risk of death during the study period (Table 4).

The ATRIA bleeding scheme. The median ATRIA score in the cohort was 1 (interquartile range: 1 to 3). The predictive performance of the ATRIA schema as reflected by the c-index were 0.50 and 0.61, for clinically relevant

Table 3 AUCs (or C-Indexes) for HEMORR$_2$HAGES, ATRIA, and HAS-BLED Scores

	Any Clinically Relevant Bleeding			Major Bleeding			Death		
AUC Analysis	AUC	95% CI	SE	AUC	95% CI	SE	AUC	95%CI	SE
HEMORR$_2$HAGES	0.55	0.51–0.59	0.019	0.60	0.51–0.69	0.046	0.57	0.50–0.65	0.033
HAS-BLED	0.60	0.56–0.63	0.019	0.65	0.56–0.73	0.043	0.67	0.60–0.73	0.035
ATRIA	0.50	0.46–0.54	0.020	0.61	0.51–0.70	0.048	0.63	0.56–0.69	0.037

AUC = area under the curve; CI = confidence interval; SE = standard error; other abbreviations as in Table 2.

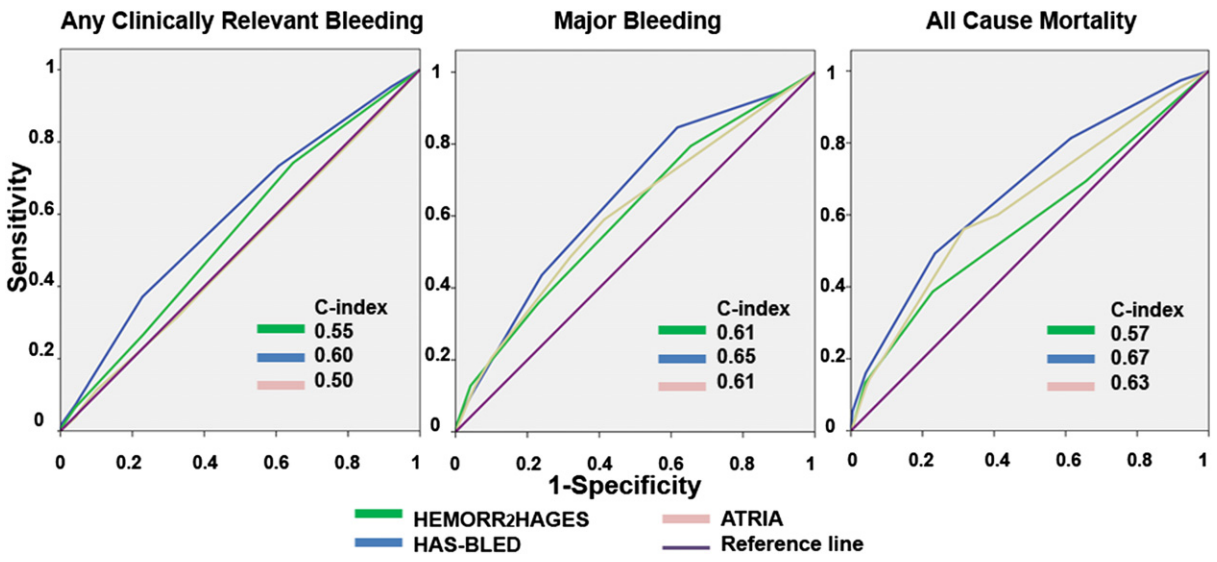

Figure 1 Receiver-Operating Characteristic Curves of the Bleeding Risk Schemes for the 3 Outcomes

The HAS-BLED score performed better for the primary endpoint of any clinically relevant bleeding compared with HEMORR$_2$HAGES (c-index: 0.6 vs. 0.55; p = 0.003) and ATRIA (0.6 vs. 0.5; p = 0.002). Further details in c-indexes comparisons are available in Tables 3 and 5. 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; 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.

bleeding and major bleeding, respectively (Table 3, Fig. 1). On Cox regression analysis, an ATRIA score >3 was not significantly associated with the risk of any clinically relevant bleeding. An ATRIA score >3 was associated with a significantly higher risk of all-cause mortality and major bleeding (Table 4, Online Fig. 1).

Comparison of bleeding schemas. The Hosmer-Lemeshow goodness-of-fit statistics supported model fit of all risk-estimation tools for both bleeding outcomes and all-cause mortality, as indicated by p values >0.05.

There were substantial differences among the 3 schemes with respect to the definition of low and intermediate/high bleeding risk. HEMORR$_2$HAGES, HAS-BLED, and ATRIA categorized 1,738 (76.6%), 1,739 (75.9%), and 2,038 (90%) patients, respectively, as low bleeding risk.

Cohen's kappa coefficient revealed poor concordance between ATRIA and the other 2 schemas (kappa: <0.2) and moderate concordance among HAS-BLED and HEMORR$_2$HAGES (kappa: 0.46). Only 56 (2.7%) patients were classified as intermediate/high risk by all 3 scores. Bleeding rates in the latter group were 5.4% and 16.1% for major bleeding and any clinically relevant bleeding, respectively, and the mortality rate was 14.3%.

The HAS-BLED score performed best in predicting any clinically relevant bleeding, reflected both on receiver-operating characteristic (ROC) analyses (Table 5) and on net reclassification improvement (Tables 6 and 7), as well as on Cox regression analysis (Table 4). On ROC analysis, the ATRIA score failed to demonstrate a significant predictive value for clinically relevant bleeding (c-index: 0.50; p = 0.87).

Using DCA, assuming that a classification of high risk by one of the tests will result in alternative treatment, HAS-BLED was superior to the "treat all alternatively" strategy for a threshold probability of any clinically relevant bleeding of 9% or more (Fig. 2). The HAS-BLED score was superior to the HEMORR$_2$HAGES and ATRIA scores for any threshold probability.

HAS-BLED performed better in predicting major bleeding events, as reflected by the slightly greater

Table 4 Cox Regression Analysis of the HEMORR$_2$HAGES, HAS-BLED, and ATRIA Score for the Outcomes of All-Cause Mortality, Major Bleeding, and Any Clinical Relevant Bleeding

	Any Clinically Relevant Bleeding		Major Bleeding		All-Cause Mortality	
Score	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
HEMORR$_2$HAGES >1	1.2 (0.9–1.5)	0.30	1.8 (0.9–3.5)	0.08	2.0 (1.3–3.3)	0.003
HAS-BLED >2	1.9 (1.4–2.4)	<0.001	2.4 (1.3–4.6)	0.006	2.9 (1.9–4.6)	<0.001
ATRIA >3	1.2 (0.8–1.7)	0.50	2.3 (1.1–5.1)	0.03	2.3 (1.3–4.0)	0.005

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

Table 5 Comparison of AUCs or C-Indexes for HEMORR$_2$HAGES, ATRIA, and HAS-BLED Scores

	Any Clinically Relevant Bleeding			Major Bleeding			Death		
Comparison	AUC Difference (95% CI)	*z* Score	p Value	AUC Difference (95% CI)	*z* Score	p Value	AUC Difference (95% CI)	*z* Score	p Value
HAS-BLED vs. HEMORR$_2$HAGES	0.04 (0.52 to 0.59)	2.95	0.003	0.04 (−0.03 to 0.12)	1.19	0.23	0.09 (−0.14 to −0.05)	4.33	<0.0001
HAS-BLED vs. ATRIA	0.09 (0.03 to 0.15)	3.14	0.002	0.04 (−0.06 to 0.14)	0.85	0.40	0.04 (−0.03 to 0.11)	1.17	0.20
ATRIA vs. HEMORR$_2$HAGES	−0.05 (−0.01 to 0.11)	−1.54	0.10	0.0 (−0.09 to 0.09)	0.04	0.97	0.05 (−0.12 to 0.02)	1.50	0.10

Abbreviations as in Tables 2 and 3.

c-index, although differences in c-index and net reclassification improvement did not reach statistical significance compared with the other 2 scores (Fig. 1). With respect to all-cause mortality, HAS-BLED performed better than HEMORR$_2$HAGES, as reflected by both c-index and net reclassification improvement, but the difference between HAS-BLED and ATRIA did not reach statistical significance.

With respect to bleeding subtypes, HEMORR$_2$HAGES and ATRIA scores did not demonstrate any significant predictive performance when fatal bleeding or intracranial hemorrhage was assessed independently (all, p = NS; full data not shown). HAS-BLED was the only score that demonstrated a significant predictive performance for intracranial hemorrhage (c-index: 0.75; 95% CI: 0.56 to 0.95; p = 0.03).

Discussion

In this study, we compared, for the first time, the HEMORR$_2$HAGES, HAS-BLED, and ATRIA scores, in predicting bleeding events in a clinical trial cohort undergoing anticoagulation. We demonstrated a clear advantage of the HAS-BLED score over both the ATRIA and HEMORR$_2$HAGES scores. Also, HAS-BLED was the only score to demonstrate a significant predictive performance for intracranial hemorrhage. An ATRIA score >3 was not significantly associated with the risk for any clinically relevant bleeding event on Cox regression or ROC analysis.

This comparison is of practical importance because bleeding risk–scoring systems are featured in management guidelines for stroke prevention in AF. The HAS-BLED scheme is recommended by the European Society of Cardiology and Canadian guidelines (5–7). The HAS-BLED score was also highlighted in the recent Royal College of Physicians of Edinburgh United Kingdom Consensus Conference on Atrial Fibrillation (7).

In our analyses, the 3 bleeding scores exhibited weak discriminatory capacity for both bleeding outcomes, as reflected by c-indexes below 0.70. Bleeding risk estimation has always been challenging and far more complicated than thromboembolic risk estimation. Even in validation cohorts (1–3), none of the bleeding risk–estimation tools exceeded a c-index of 0.74 despite the numerous risk factors incorporated for their calculation (13 for HEMORR$_2$HAGES, 8 for HAS-BLED, and 5 for ATRIA). However, the c-index is not the only parameter to be taken into consideration in determining the utility or predictive ability of risk-estimation schemas (8). From the clinical perspective, reclassification analysis seems to be of greater importance, especially for patients reclassified correctly from low-

Table 6 Reclassification Table for Any Clinical Relevant Bleeding Risk Estimated by HAS-BLED, HEMORR$_2$HAGES, and ATRIA Schemas

			HAS-BLED			HEMORR$_2$HAGES		
			High	Low	Total	High	Low	Total
ATRIA								
	High	Event	18	10	28	10	18	28
		No Event	67	135	202	83	119	202
	Low	Event	74	146	220	56	164	220
		No Event	393	1,425	1,818	381	1,437	1,818
	Total	Event	92	156	248	66	182	248
		No Event	460	1,560	2,020	464	1,556	2,020
HEMORR$_2$HAGES								
	High	Event	54	12	66			
		No Event	306	154	460			
	Low	Event	38	144	182			
		No Event	158	1,402	1,560			
	Total	Event	92	156	248			
		No Event	464	1,556	2,020			

Abbreviations as in Table 2.

Table 7 NRI Analysis for the Outcomes of Any Clinically Relevant Bleeding, Major Bleeding, and All-Cause Mortality

	Any Clinically Relevant Bleeding			Major Bleeding			All-Cause Mortality		
Comparison	NRI	*z* Score	p Value	NRI	*z* Score	p Value	NRI	*z* Score	p Value
HAS-BLED vs. HEMORR$_2$HAGES	0.103	3.45	<0.001	0.068	0.80	0.42	0.099	2.32	0.02
HAS-BLED vs. ATRIA	0.13	3.37	<0.001	0.090	0.97	0.33	0.139	1.94	0.05
ATRIA vs. HEMORR$_2$HAGES	0.021	0.596	0.55	−0.022	0.227	0.82	0.040	0.55	0.58

NRI = net reclassification improvement; other abbreviations as in Table 2.

intermediate risk to high risk, as these patients will be considered for alternative treatment.

With respect to the principal outcome of any clinically relevant bleeding, the ATRIA score failed to demonstrate any additional predictive value over chance alone, whereas HEMORR$_2$HAGES was slightly better than random stratification. HAS-BLED was significantly better than the other 2 scores in predicting any clinically relevant bleeding. Using DCA, the HAS-BLED score performance was superior to that of HEMORR$_2$HAGES and ATRIA with respect to its clinical applicability for whole-spectrum threshold probabilities.

The fact that HAS-BLED exhibited predictive capacity for clinically relevant bleeding should be considered as an advantage, especially because nonmajor clinically relevant bleeding may significantly influence outcome by interrupting or affecting the quality of anticoagulation. Also, only HAS-BLED had a significant (and "good," c-index: 0.75) predictive ability for intracranial hemorrhage, a potential effect of oral anticoagulation. With respect to major bleeding events, all 3 scores demonstrated significant predictive ability, although their c-indexes were below the cutoff point of what is considered good performance (c-index: <0.70). No statistically significant differences were observed between the 3 scores in the outcome of major bleeding.

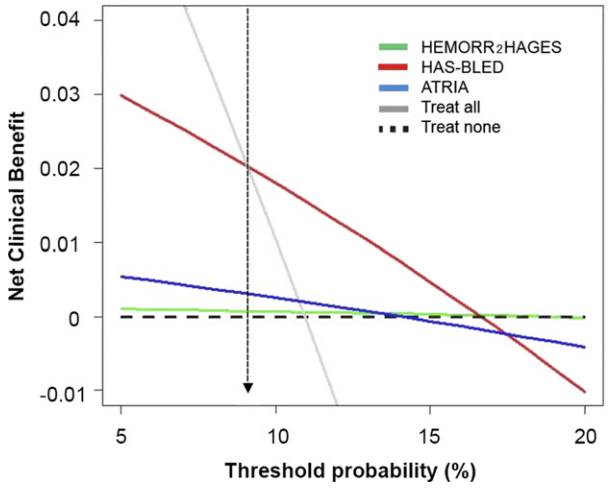

Figure 2 Decision Curve Analysis: Net Number of True Positives Gained Using a Model Compared to No Model at a Range of Thresholds Probabilities

We assume that a classification of high risk on one of the tests will result in alternative treatment. If it is considered efficient to apply alternative treatment in 11 patients or less to prevent 1 clinically relevant bleeding event (i.e., threshold probability 9%; **dotted arrow**), then HAS-BLED is superior to the "treat all alternatively" strategy **(gray line)** and the "treat none alternatively" strategy **(black dotted line)**. The HAS-BLED score was also superior to the HEMORR$_2$HAGES and ATRIA scores for any threshold probability. For a threshold probability of <9%, the "treat all alternatively" strategy provides the highest net clinical benefit. Abbreviations as in Figure 1.

Mortality prediction. Bleeding risk–prediction schemes were not developed to predict mortality, although major bleeding and mortality are closely related endpoints in populations undergoing anticoagulation (9). In our analysis, the HAS-BLED score performed best in predicting all-cause mortality, as reflected by the c-index, followed by the ATRIA score. The HEMORR$_2$HAGES score had the worst performance, probably due to the larger number of bleeding-oriented factors that are used for its calculation.

Study limitations. These are results of a post hoc analysis and they should be interpreted as such. The AMADEUS trial population was at relatively low risk for both ischemic stroke and bleeding events compared with patients in clinical practice; patients with a history of major bleeding events or who are at risk for bleeding were excluded from the study. It remains to be established whether these risk scores would have a similar accuracy in clinical practice. Finally, this was a retrospective analysis, and no available trials have evaluated prospectively the impact of the use of these 3 bleeding risk–estimation schemes on patient outcomes (10).

Conclusions

All 3 tested bleeding risk–estimation scores demonstrated only modest performance in predicting the outcome of any clinically relevant bleeding, although the HAS-BLED score performed better than the HEMORR$_2$HAGES and ATRIA scores, as reflected by ROC analysis, reclassification analysis, and DCA. Only HAS-BLED demonstrated a significant predictive performance for intracranial hemorrhage. Given its simplicity, the HAS-BLED score may be an attractive method for the estimation of oral anticoagulant–related bleeding risk for use in clinical practice, supporting the recommendations in the international guidelines.

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Key Words: AMADEUS trial ■ ATRIA ■ atrial fibrillation ■ bleeding ■ HAS-BLED ■ HEMORR$_2$HAGES.

APPENDIX

For supplementary tables and figures, please see the online version of this article.