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Original Article

Performance of HAS-BLED and DOAC scores to predict major bleeding events in atrial fibrillation patients treated with direct oral anticoagulants: A report from a prospective European observational registry

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ABSTRACT

Background: The DOAC score has been recently proposed for bleeding risk stratification of patients with atrial fibrillation treated with direct oral anticoagulants (DOAC).
Objective: To compare the performance of HAS-BLED and DOAC score in predicting major bleeding events in a contemporary cohort of European AF patients treated with DOAC.
Methods: We included patients derived from a prospective observational registry of European AF patients. HAS-BLED and DOAC scores were calculated as per the original schemes. Our primary endpoint was major bleeding events. Receiver operating characteristic (ROC) curves were used to compare the predictive ability of the scores.
Results: A total of 2834 AF patients (median age [IQR] 69 [62–77] years; 39.6 % female) treated with DOAC were included in the analysis. According to the HAS-BLED score, 577 patients (20.4 %) were categorized as very low risk of bleeding, as compared to 1276 (45.0 %) according to DOAC score. A total of 55 major bleeding events occurred with an overall incidence of 1.04 per 100 patient-years. Both scores showed only a modest ability for the prediction of bleeding events (HAS-BLED area under the curve [AUC], 0.65, 95 % confidence interval [CI] 0.55–0.70; DOAC score AUC 0.62, 95 % CI 0.59–0.71, p for difference = 0.332]. At calibration analysis, the DOAC score showed modest calibration, especially for patients at high risk, when compared to HAS-BLED.
Conclusion: In a contemporary cohort of DOAC-treated AF patients, both HAS-BLED and DOAC scores only modestly predicted the occurrence of major bleeding events. Our results do not support the preferential use of DOAC score over HAS-BLED.

Abbreviations: AF, atrial fibrillation; aHR, adjusted hazard ratio; APT, antiplatelet; AUC, area under the curve; BMI, body mass index; CI, confidence interval; CG, Cockroft Gault; CKD, chronic kidney disease; CrCl, creatinine clearance; DOAC, direct oral anticoagulant; FU, follow-up; HR, hazard ratio; ICH, intracranial hemorrhage; IDI, integrated discrimination improvement; IQR, interquartile range; IR, incident rate; LVEF, left ventricular ejection fraction; MI, median improvement; NRI, net reclassification improvement; OAC, oral anticoagulant; SD, standard deviation; ROC, receiver operating characteristic; TE, thromboembolic events; VKA, vitamin K antagonist.

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1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia worldwide and it is associated with a 3–5-fold higher risk of stroke [1]. This risk has been significantly reduced after the introduction of oral anticoagulants (OAC), that should be prescribed in all patients who are not considered at very low-risk of thromboembolism (i.e.: CHA_2DS_2-VASc Score 0 in males and 1 in females) as recommended by current guidelines on AF [2–5].

Bleeding is a known possible complication of OAC therapy. Therefore bleeding risk assessment is one of the main steps in the evaluation of patients with AF [6].

In the past years, several clinical scores have been developed to stratify the risk of bleeding of AF patients undergoing OAC therapy [7–9]. One of the most commonly used scores in clinical practice is the HAS-BLED score, which have been extensively validated in different AF cohorts worldwide ([4,10–12]). The HAS-BLED score was developed at a time when the majority of AF patients were prescribed with vitamin K antagonists (VKAs). Other scores that were subsequently developed to assist physician's decision making are ORBIT [8], HEMORR2HAGES [13] and ATRIA [14], all showing only a modest predictive ability in the prediction of major bleeding events. The use of HAS-BLED is endorsed by European guidelines, while the recently published American guidelines on AF do not support the preferential use of one score over another ([2,3]).

All previous scores have been developed and validated in a period where AF patients were mainly prescribed with VKAs [15]. However, in recent years, direct oral-anticoagulants (DOACs) emerged as an alternative to VKAs, and became the most commonly prescribed anticoagulant drugs in AF patients, especially for their lower bleeding risk [16–21].

To better predict the risk of bleeding in AF patients treated with DOACs, a new score called the DOAC score was recently developed and validated [22]. This score showed an increase in the predictive ability of major bleeding events in the development and derivation cohorts. Nonetheless, the overall ability of the score to predict major bleeding events was still modest, albeit statistically superior to the HAS-BLED score. Since this is a recently developed score, data are still lacking regarding its performance in different cohorts of patients. Therefore, the aim of the present study is to compare the performance of the new DOAC score with the established HAS-BLED score in the stratification of bleeding risk in a large prospective real-world cohort of European AF patients.

2. Methods

2.1. Population of the study

We included patients with AF from a large, prospective, observational registry held in Europe. Details on the study design, patient baseline characteristics and primary outcomes have been previously published ([16,23]). Briefly, the registry enrolled consecutive adult patients (age $\geq$ 18 years) with an ECG-documented episode of AF in the 12 months before the inclusion, who provided written informed consent. Patients were enrolled in 250 participating centers across 27 countries between October 2013 and September 2016, with a pre-planned 2-year follow-up until September 2018. At enrollment, baseline characteristics, previous medical history and pharmacological treatment of each patient were collected by the investigator and reported using a standardized electronic case report form. The study protocol was approved for each country and for each enrolling site by the National Coordinators' main institutions. The study was performed according to the European Union Note for Guidance on Good Clinical Practice CPMP/ECH/135/95 and the Declaration of Helsinki.

For the purpose of this analysis, we included all AF patients treated with DOACs, with available data regarding HAS-BLED and to calculate DOAC score, and with available follow-up data regarding the occurrence of major bleeding events. Thromboembolic risk of patients was defined according to CHA_2DS_2-VASc score, while AF was categorized according to the 4s scheme of the 2020 ESC guidelines, i.e.: first diagnosed, paroxysmal, persistent, long-standing persistent, and permanent [2]. Symptomatic status was defined according to the guideline recommended EHRA score.

2.2. Bleeding scores

HAS-BLED and DOAC scores were calculated in our cohort of patients based on their original definitions ([7,22]) (Supplementary Method). In our registry, HAS-BLED was originally calculated and reported in the electronic case report form by the investigator, at the moment of the enrollment. Conversely, we calculated the DOAC score retrospectively (based on the criteria defined in the validation study [22]) using baseline patient characteristics reported into the final dataset.

We categorized patients as: (i) *very low* risk for HAS-BLED = 0 and for DOAC score = 0–3; (ii) *low* risk for HAS-BLED = 1 and for DOAC score = 4-5; (iii) *moderate* risk, for HAS-BLED = 2 and for DOAC score = 6-7; (iv) *high* risk, for HAS-BLED $\geq$3 and for DOAC score = 8–10; compared to the original proposal of the DOAC score [22], we lumped the "high" (DOAC score 8-9) and "very high" (DOAC score = 10) groups into the "high risk" group, in view of the small number of patients with DOAC score = 10.

Information regarding the method used to calculate both scores are reported in the supplementary material (Supplementary Method).

2.3. Follow up and bleeding events

As per the original study design, all patients discharged alive were followed-up for 2 years after enrollment, and the incidence of major adverse events was recorded. Details regarding the follow-up procedures have been already reported elsewhere [16].

For this analysis, major bleeding was considered our primary endpoint and was defined as a composite of any intracranial hemorrhage (ICH) and major extracranial bleeding. Major extracranial bleeding included bleeding event causing a drop in hemoglobin level $\geq$ 2 g/dl, requiring blood transfusion or hospitalization, occurring in any major organ system, as defined by the International Society on Thrombosis and Haemostasis [24]. We also reported the occurrence of all-cause death and stroke as a secondary analysis.

2.4. Statistical analysis

Continuous variables were reported as median and interquartile range (IQR) or as mean and standard deviation (SD). Categorical variables were reported as counts and percentages. We calculated incidence rate (IR) per 100 person-year of major bleeding events according to the 4 different risk categories for the two scores. Cumulative survival according to bleeding scores categories was assessed using Kaplan-Meier curves and tested for difference using the log-rank test. Univariable and multivariable Cox regression analyses were used to evaluate the association between major bleeding events and HAS-BELD and DOAC score used as continuous variables and also categorical variables (high-risk *vs.* low/intermediate risk categories and also stratified according the prespecified different categories). Variables included in the Cox regression model were female sex, type of AF and EHRA score.

To compare the predictive performance of the two scores, we used receiver operating characteristic (ROC) curves and calculated the area under the curve (AUC) with its 95 % confidence intervals (CIs) with regard to prediction of major bleeding. Comparisons between the two AUCs were estimated using the method proposed by DeLong and DeLong

[25]. As sensitivity analysis we also used ROC curves for major bleeding in the population of patients aged 75 years or more.

We also produced calibration plots, plotting the IR of bleeding events for each score category in our cohort against those reported in the original derivation cohort of the two scores ([7,22]).

Adopting the method described by Pencina et al. [26], we performed reclassification analyses with HAS-BLED as reference. We calculated the integrated discrimination improvement (IDI), net reclassification improvement (NRI) and median improvement (MI) both at 1 year and 2-year follow-up. Lastly, decision curve analysis was performed [27]. Two-sided P-values <0.05 were considered statistically significant. All analyses were performed using R 4.2.2 for MacOS using the pROC [28], rms, rmda and survIDINRI packages.

3. Results

From the original cohort of 11,096 patients enrolled in the registry, 5553 patients were excluded because treated with VKAs and 1653 because not treated with oral anticoagulants. 894 have been excluded due to lack of data regarding the variables used to calculate the DOAC score and 156 because of missing information on major bleeding events occurrence. Finally, 2834 AF patients (median age [IQR] 69 [62–77] years; 39.6 % female) treated with DOAC were included in the analysis. Table 1 shows the baseline characteristics of the population included. The median [IQR] CHA_2DS_2-VASc of the population was 3 [2–4], and the majority of patients had paroxysmal or persistent AF (27.6 % and 27.9 %, respectively). Only 8.5 % of the population included was concomitantly treated with an antiplatelet agent.

Supplementary Table 1 shows the differences in baseline characteristics between the patients included and excluded from the present analysis. Individuals excluded were older and had a higher prevalence of coronary artery disease and of malignancy. No other significant differences were found.

Table 2 shows the distribution of bleeding scores. The mean HAS-BLED score was 1.33 (SD 0.98) (median [IQR] 1 [1-2]). Conversely, the mean DOAC score was 3.95 (SD 2.64) (median 4 [2–6]). According to HAS-BLED, 577 (20.4 %) patients were considered at very low risk and 329 (11.6 %) at high risk. Using the DOAC score, 1276 (45 %) patients were categorized as very low risk, while 254 (9.0 %) at high risk.

The characteristics of the population according to the categories of the two scores are reported in Supplementary Tables 2 and 3. Patients categorized as "very low-risk" according to HAS-BLED were younger and with lower prevalence of most comorbidities.

Table 1
Baseline characteristics of the population included in the analysis.

Characteristics	Population
	$N = 2834$
Age (years) (median [IQR])	69.00 [62.00, 77.00]
Female, N (%)	1104 (39.0)
HAS-BLED, mean (SD)	1.33 (0.98)
DOAC score, mean (SD)	3.95 (2.64)
BMI (median [IQR])	27.80 [24.92, 31.50]
CrCl-CG (median [IQR])	77.87 [58.39, 100.39]
LVEF (%) (median [IQR])	56.00 [47.00, 62.00]
AF type (%)	
Paroxysmal	774 (27.6)
Persistent	782 (27.9)
Long standing	121 (4.3)
Permanent	518 (18.5)
First diagnosed	605 (21.6)
Hypertension, N (%)	1718 (60.6)
Diabetes mellitus, N (%)	579 (20.4)
Dyslipidemia, N (%)	1100 (39.9)
Coronary artery disease, N (%)	579 (21.1)
Peripheral vascular disease, N (%)	177 (6.3)
Heart Failure, N (%)	870 (30.9)
Previous TE events, N (%)	329 (11.6)
Previous haemorrhagic events, N (%)	153 (5.4)
CKD, N (%)	286 (10.1)
Liver disease, N (%)	45 (1.6)
Anemia, N (%)	93 (3.3)
Malignancy (current+prior), N (%)	247 (8.8)
CHA2DS2-VASc (median [IQR])	3.00 [2.00, 4.00]
Concomitant APT	
None	2594 (91.5)
Only Aspirin	175 (6.2)
Aspirin+P2Y12 inhibitor	65 (2.3)

AF, atrial fibrillation; BMI, body mass index; APT, antiplatelet; CG, Cockroft Gault; CKD, chronic kidney disease; CrCl, creatinine clearence; LVEF, left ventricular ejection fraction; TE, thromboembolic events.

3.1. Follow-up and major bleeding events

After a median [IQR] follow-up of 731 [701-751] days, a total of 55 major bleeding events occurred (9 intracranial bleeding and 46 major extracranial hemorrhages), with an overall incidence of 1.04 per 100 patient-years. Table 2 reports the IR per 100 person-years according to different bleeding risk categories. The IR of major bleeding showed a constant graded increase across risk categories of the HAS-BLED score. On the other hand, a less evident increase in IR was seen between the very low and low risk categories for DOAC score, followed by an increase for the medium and high-risk categories (Table 2).

Also, 52 ischemic stroke events occurred during the 2 years follow up with an IR of 0.98 per 100 patients-years. There were 209 all-cause deaths with an IR of 3.90 per 100 patient-years.

3.2. Risk of bleeding according to scores

Kaplan-Meier curves showed that patients categorized as high-risk according to both HAS-BLED and DOAC score had a higher cumulative incidence of major bleeding events (Fig. 1). Consistently, a significant association was found both at univariable and multivariable Cox regression analysis between the 2 scores used as continuous variables and the risk of major bleeding events.

High bleeding risk categories showed a significant association with major bleedings on univariable analysis (hazard ratio [HR] 2.03, 95 % CI 1.05–3.92 for HAS-BLED and HR 2.46, 95 % CI 1.24–4.88 for DOAC

Table 2
Bleeding score distribution and incidence of major bleeding.

	HAS-BLED score		DOAC score	
Median [IQR]	1.00 [1.00, 2.00]		4.00 [2.00, 6.00]	
Bleeding risk category				
	N, (%)	**IR/100 p-years**		**IR/100 p-years**
Very-low	577 (20.4)	0.18	1276 (45.0)	0.74
Low	1141 (40.3)	0.88	676 (23.9)	0.78
Medium	787 (27.8)	1.60	628 (22.2)	1.47
High	329 (11.6)	1.91	254 (9.0)	2.33

Bleeding risk categories are defined as: very-low, 0 for HAS-BLED and 0-3 for DOAC score; low, 1 for HAS-BLED and 4-5 for DOAC score; moderate, 2 for HAS-BLED and 6-7 for DOAC score; high, ≥3 for HAS-BLED and 8-10 for DOAC score.
IQR, interquartile range; IR, incidence rate; p, person.

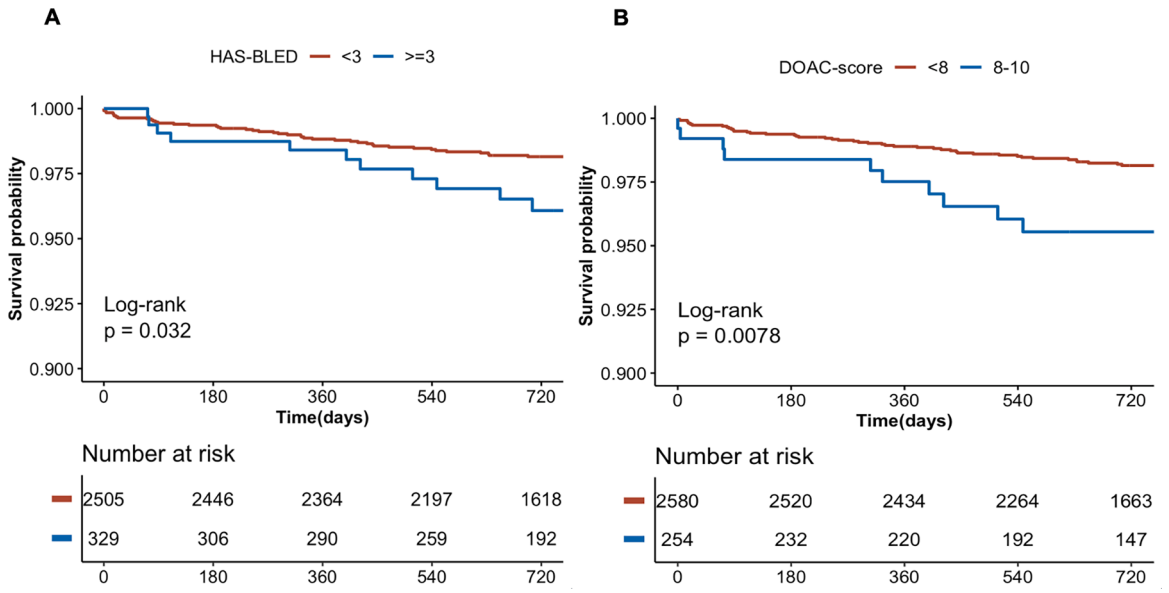

Fig. 1. Kaplan-Meier curves for Major Bleeding. Panel A shows the cumulative incidence of major bleeding events categorized by HAS-BLED. Panel B shows the cumulative incidence of major bleeding events categorized by DOAC score.

Table 3
Cox regression analysis for major bleeding.

	Univariable		Multivariable*	
	HR [95 % CI]	P value	aHR [95 % CI]	P value
HAS-BLED				
Continuous	1.72 [1.35-2.19]	**<0.001**	1.66 [1.29-2.14]	**<0.001**
≥3 (vs < 3)	2.03 [1.05-3.92]	**0.036**	1.80 [0.92-3.52]	0.087
DOAC score				
Continuous	1.19 [1.08-1.32]	**<0.001**	1.17 [1.05-1.30]	**<0.001**
≥8 (vs < 8)	2.46 [1.24-4.88]	**0.010**	2.04 [0.99-4.18]	0.052

aHR, adjusted hazard ratio; CI, confidence interval; HR hazard ratio.
* Model adjusted for sex, EHRA score and type of atrial fibrillation

score), but this association was not statistically significant after adjustments for female sex, EHRA score, and type of AF for high risk patients for both HAS-BLED ($P = 0.087$) and for DOAC scores ($P = 0.052$), although point estimates were suggestive of higher risk (Table 3).

The risk of bleeding progressively and significantly increased according to the different categories defined by HAS-BLED compared to the very low-risk group (Supplementary Fig. 1 and Supplementary Table 4). Conversely, only patients considered at high-risk according to the DOAC score showed a significant increase in the risk of bleeding (Supplementary Table 5).

3.3. *Predictive performance, reclassification analysis and calibration plots*

Fig. 2 shows the ROC curves for HAS-BLED and DOAC scores. Both had a moderate performance in the prediction of major bleeding events. HAS-BLED had a numerically higher AUC value (AUC 0.649, 95 % CI 0.586–0.711) as compared to DOAC score (AUC 0.621, 95 % CI 0.547–0.696), as also suggested by the visual inspections of the two ROC curves. The difference between HAS-BLED score and DOAC score was not statistically significant using the DeLong and DeLong test (P for difference=0.332).

Being at very low-risk according to HAS-BLED score showed a very high specificity for the prediction of absence of bleeding (98 %), while only a modest specificity was found for the very low-risk category according to DOAC score (67 %) (Supplementary Table 5). Both very low-risk categories showed a poor sensitivity for the prediction of no bleeding at follow-up (21 % for HAS-BLED, 45 % for DOAC score). Supplementary Table 6 shows the predictive characteristics for the occurrence of major bleeding according to the high-risk category. High-risk class for both HAS-BLED and DOAC score showed high specificity (89 % and 91 %, respectively), albeit at the cost of a poor sensitivity (20 % and 18 %, respectively).

Also the sensitivity analysis conducted on the population 75 years or more, showed a non-significant difference between the ROC curves for major bleeding calculated for DOAC and HAS-BLED scores, (AUC 0.652, 95 % CI 0.552–0.753, AUC 0.626, 95 % CI 0.523–0.738, respectively, P for difference=0.553, Supplementary Fig. 2), thus providing an additional evaluation for the subgroup of older patients.

Results of reclassification analyses are reported in Table 4. Projecting the risk stratification at both 1 year and 2 years of follow-up, we did not find a significant difference between the two scores in terms of IDI, NRI and MI. These results were consistent also with the decision curve analysis (Supplementary Fig. 3) that did not show any difference in net benefit using HAS-BLED or DOAC score.

At model calibration analysis comparing IR of major bleeding events in our cohort of patients with those reported in the original derivation cohorts ([7,22]), both HAS-BLED and DOAC score showed a good calibration for the low-risk strata, while only poor calibration was found for the higher risk categories (Fig. 3). Compared with HAS-BLED, DOAC score had poorer calibration, especially for the high-risk values of the score.

4. Discussion

The main results of our analysis are as follows: (i) the incidence of major bleeding events in a contemporary cohort of DOAC treated AF patients was low, (ii) both HAS-BLED and DOAC scores showed a significant association with the risk of major bleeding events, with only modest predictive ability, (iii) as compared to DOAC score, HAS-BLED better identified patients at very low risk of bleeding; (iv) reclassification analysis did not show a significant difference between the two scores, but compared with HAS-BLED, DOAC score had poorer calibration especially for those at high-risk. Hence, our results do not support the preferential use of one score over the other.

To the best of our knowledge, this is one of the first analysis comparing the newly developed DOAC score with the HAS-BLED score after the publication of the validation analysis [22]. Our results add a

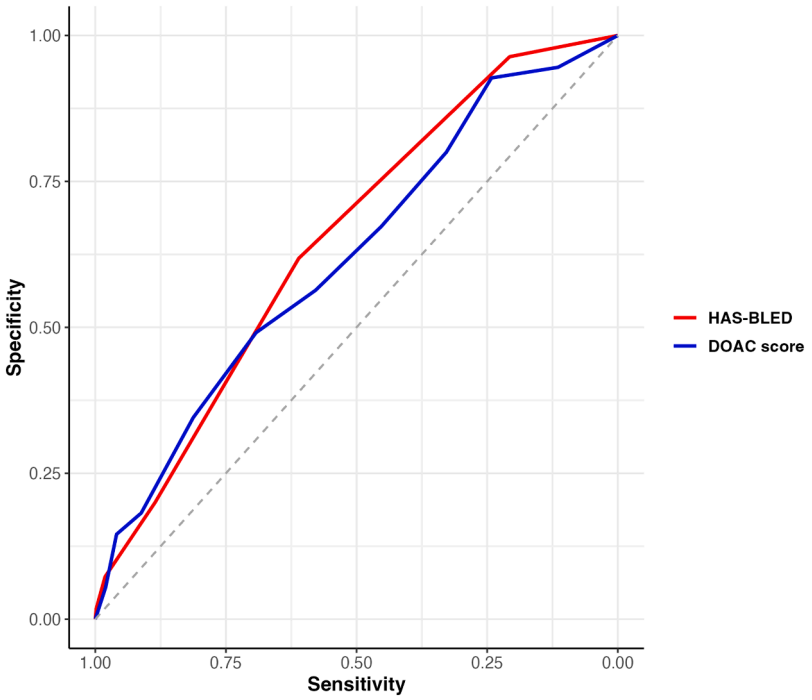

Fig. 2. Area under the curve for prediction of Major Bleeding for HAS-BLED and DOAC score
AUC [95 % CI] HAS-BLED score: 0.65 [0.55-0.70];
AUC [95 % CI] DOAC score: 0.62 [0.59-0.71].
DeLong's test for difference: Z = -0.97, p-value = 0.332
AUC, area under the curve; CI, confidence interval.

Table 4
Reclassification analysis for bleeding risk scores for major bleeding occurrence.

DOAC score *vs.* HAS-BLED score	IDI (95 % CI)	P- value	NRI (95 % CI)	P- value	MI (95 % CI)	P- value
1-year FU	-0.001 (-0.010/0.002)	0.571	-0.091 (-0.258/0.078)	0.299	0.000 (-0.003/0.002)	0.080
2-year FU	-0.003 (-0.014-0.004)	0.312	-0.111 (-0.266/0.124)	0.233	0.000 (-0.007/0.004)	0.166

CI, confidence interval; FU, follow-up; IDI, integrated discrimination improvement; MI, median improvement; NRI, net reclassification index.

further evaluation regarding the performance of the two scores using data derived from a spontaneous study and with an independent setting. This is important since DOAC-treated patients have a higher bleeding incidence rate in real-world cohorts as compared to clinical trials, and this is related to inclusion of older patients with a higher burden of co-morbidities [29].

In our cohort of patients, the incidence of major bleeding was low. This finding may be explained by the fact that DOAC therapy has become the recommended treatment for AF patients over the VKAs in many clinical guidance worldwide [4]. The advantage of DOAC as compared with VKA includes a comparable efficacy in terms of reducing the risk of stroke, with a superior profile in terms of safety and major bleeding (especially for ICH bleeding) [30]. Compared with our study, a similar rate of bleeding was also reported in other large registries of AF patients. In the GLORIA-AF registry, the incidence of major bleeding was 0.97 per 100 patients-years [31]. Consistently, in an edoxaban-treated AF population, the annualized event rate of major bleeding events was 1.73 %/year for patients with HF vs. 0.86 %/year for no-HF patients [32]. Another possible explanation of the low incidence of major bleeding events is related to the observational nature of our study, and the absence of adjudication of adverse events.

An additional possible explanation may be related to the type of population included in our analysis as compared to previous ones. In our study, individuals' median age was 69 years, which is lower as compared with previous populations from the phase III trials with DOAC [33–36] and also with other observational real-word registries conducted in Europe ([37,38]). This point may limit the generalizability of our findings; however, as shown by the sensitivity analysis, the performance of DOAC score and HAS-BLED score were similar also in the population of patients aged 75 years or more. This suggests that our main findings are not markedly conditioned by the relatively younger age characterizing our population.

Since bleeding is a known and feared complication of DOAC therapy, hemorrhagic risk assessment has become a key step in the evaluation of AF patients [4]. Many clinical risk scores have been developed throughout the years, although all of them showed only a modest predictive ability [39]. In line with previous validated scores, the new DOAC score showed a statistically significant superiority as compared to HAS-BLED score in both derivation and validation cohorts [22], albeit the main limitation still stands in the absolute modest improvement (at least statistically) in the prediction of major bleeding events. This fact is not particularly surprising and the widespread use of clinical risk scores has been limited by their modest capability of predicting adverse outcomes [40]. Efforts to improve scores, also by adding biomarkers, only slightly improved the performance of different scores, but at the price of reduced simplicity and widespread use [41].

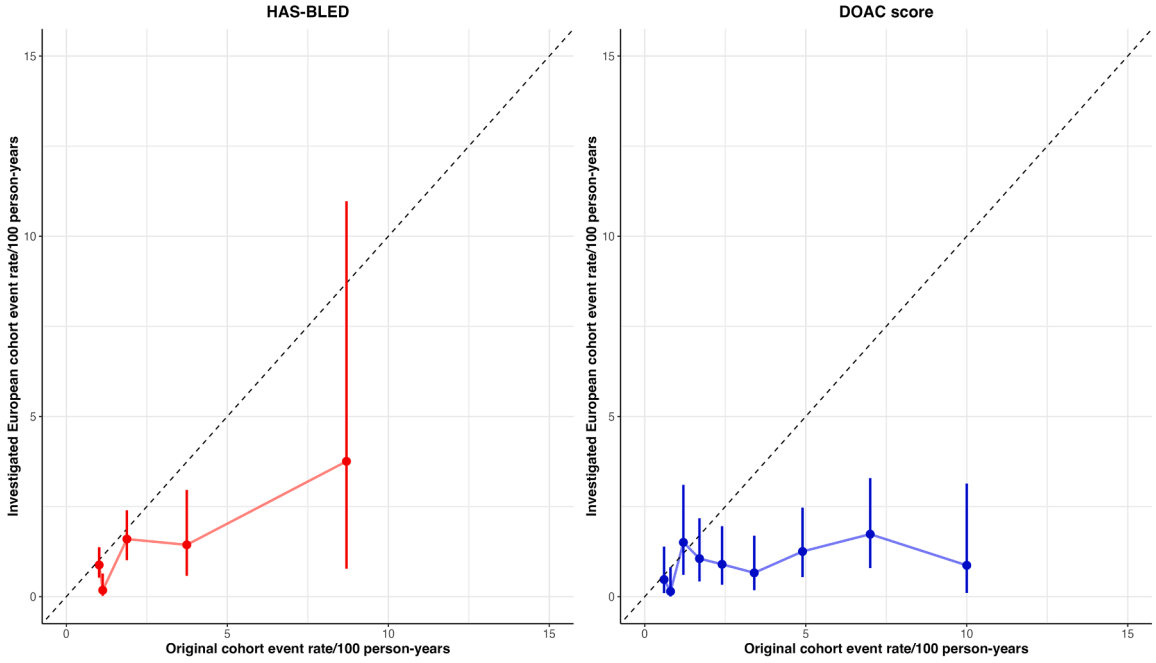

Fig. 3. Calibration curves for bleeding risk scores plotted against original derivation cohorts.
HAS-BLED score=5 was not included in the plot because low numbers of patients in the category.

The novelty of DOAC score stands in the fact that it has been developed in a cohort of patients treated only with DOAC agents, while previous scores have been created and validated in AF patients mainly treated with VKAs. Of note, variables included in the DOAC score are mainly non-modifiable risk factors and this may represent a downside, especially since bleeding risk is the interaction of modifiable and non-modifiable factors.

Indeed, current recommendations for prescribing OACs in AF patients are not based on bleeding scores and a high score does not contraindicate OAC therapy ([2,4,42]). With this perspective, bleeding scores remind physicians to address modifiable risk factors for bleeding and to manage AF patients with a holistic and integrated approach [43–46]. Notably both scores included the evaluation of concomitant antiplatelet therapy, which may increase the risk of bleeding [47]. The strength of HAS-BLED score is that it includes both modifiable and non-modifiable risk factors that can be addressed and corrected during follow-up of AF patients [48].

One interesting results of our analysis is that, when considering a cut-off of HAS-BLED score of 0, we identified 577 patients considered at very low-risk (20.4 % of the whole cohort). Conversely, patients classified as very low-risk according to DOAC score were 1276, almost a half of the population analyzed (45.0 %). As a consequence, a HAS-BLED score of 0 showed a very high specificity (98 %) for the prediction of absence of major bleeding at follow-up, which was considerably higher compared to a DOAC score between 0 and 3 (specificity 67 %). This finding may suggest that HAS-BLED may provide higher specificity compared to DOAC score in terms of identifying patients at very low-risk of experiencing major bleeding events, thus improving the ability of the clinician to better balance thromboembolic and bleeding risks. Notwithstanding this, the bleeding risk is dynamic and changes over time, and a time-dependent increase of HAS-BLED score may result as a valuable predictor of major bleeding events [49]. Consequently, a periodic reassessment of bleeding risk factors is strongly recommended by current clinical guidelines [4].

One of the possible advantages of the DOAC score is that it includes variables that describe patients' metabolic status (e.g.: diabetes, hypertension, and BMI). An unhealthy metabolically status was recently associated with an increased risk of major bleeding for all BMI categories, stressing the need for a holistic and integrated approach to be applied to all the categories of AF patients [50–53].

Lastly, in our cohort of AF patients treated with DOAC, we did not find a statistically significant difference between the two scores at reclassification analysis, suggesting a similar performance of the HAS-BLED and DOAC score. These findings should be interpreted considering that in our cohort both HAS-BLED and DOAC scores showed a good calibration only for the lower values of the scores. Of note, HAS-BLED score has been extensively validated in different patient populations worldwide, treated with different antithrombotic regimens, and has a similar or better prediction ability of major bleeding events as compared also to other scores [54]. Since the DOAC score has been validated and tested in patients treated with DOACs, its value will have to be reassessed in case of widespread implementation of Factor XI/XIa inhibitors [55].

5. Study limitations

Our study has some limitations that should be acknowledged. The main limitation is related to the observational nature of our analysis. Hence, possible bias may be present in the interpretation of our findings. As already reported, the absence of a central adjudication of events, with an investigator-based reporting of adverse outcomes, may have limited the number of reported major bleeding events, thus being another possible limitation of the study. However, the event "major bleeding" as defined in our analysis (composite of ICH and clinically relevant extracranial bleeding) usually has severe consequences on the health of the individuals, thus increasing the probability of a correct reporting. Notably, we considered major bleeding events during the overall 2-year follow-up of the study, while in the original DOAC score derivation study [22], major bleeding events at 1-year were considered. Since the overall incidence of major bleeding event was low, the analysis on prediction and reclassification may has been limited.

One more limitation derives from the number of patients that have been excluded from the analysis, that may limit the interpretation of our study findings with regard to extrapolation to much older patient populations. However, in order to add another evaluation, valuable for older patients, we analyzed the ROC curves of HAS-BLED and DOAC scores for

predicting major bleeding events in the specific subset of patients aged 75 years or older. The similar performance of the two scores in older patients suggests that our main findings are not markedly conditioned by the median age of 69 years characterizing our population.

6. Conclusions

In a contemporary cohort of AF patients treated with DOAC, both HAS-BLED and DOAC scores only modestly predicted the occurrence of major bleeding events. The DOAC score had poorer calibration especially for those at high-risk when compared to HAS-BLED score. Our results do not support the preferential use of DOAC score over HAS-BLED. The similar performance of the two scores in patients aged 75 years or older suggests that our main findings are not markedly conditioned by the relatively young age characterizing our population.

Declaration of competing interest

GB: reports small speaker fees from Bayer, Boehringer Ingelheim, Boston, BMS, Daiichi, Sanofi and Janssen outside the submitted work.

GYHL: Consultant and speaker for BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, Anthos. No fees are received personally. He is a National Institute for Health and Care Research (NIHR) Senior Investigator and co-PI of the AFFIRMO project on multimorbidity in AF (grant agreement No 899871), TARGET project on digital twins for personalised management of atrial fibrillation and stroke (grant agreement No 101136244) and ARISTOTELES project on artificial intelligence for management of chronic long term conditions (grant agreement No 101080189), which are all funded by the EU's Horizon Europe Research & Innovation programme.

MP: Italian national Principal Investigator of the AFFIRMO project on multimorbidity in atrial fibrillation, which has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No 899871.

GFR: GFR reports consultancy for Boehringer Ingelheim and an educational grant from Anthos, outside the submitted work. No fees are directly received personally.

The other authors do not have conflict of interests to report.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2024.06.022.

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