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Comparison of HAS-BLED and ORBIT Bleeding Risk Scores in AF Patients treated with NOACs: A Report from the ESC-EHRA EORP-AF General Long-Term Registry

--Manuscript Draft--

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Abstract:	Introduction: Bleeding risk assessment is recommended in guidelines for the management of atrial fibrillation (AF). HAS-BLED score was proposed prior to non-vitamin K antagonist oral anticoagulants (NOACs) and has been suggested that the ORBIT score may be superior in predicting bleeds in NOAC users. We aimed to compare the HAS-BLED and ORBIT scores in contemporary AF patients treated with NOACs. Methods and Results: We analyzed patients enrolled in the ESC-EHRA EORP-AF General Long-Term Registry. HAS-BLED and ORBIT scores were computed based on original schemes. The primary outcome was the occurrence of Major Bleeding (MB). A total of 3018 patients (median age 70; 39.6% females) were included: median [IQR] HAS-BLED and ORBIT scores were 1 [1-2] and 1 [0-2], respectively; 356 (11.8%) patients were at high risk for MB using HAS-BLED (≥3) and 123 (4.1%) using ORBIT (≥4). Overall, 60 (2.0%) MB events were recorded, with an incidence of 1.1 per 100 patient-years. Both HAS-BLED and ORBIT were associated with outcome, modestly predicting MB (AUC 0.653, 95% CI 0.593-0.714 and AUC 0.601, 95% CI 0.526-0.677, respectively). Calibration plots showed that both scores were poorly calibrated, particularly the ORBIT score, which showed consistent poorer calibration. Time-dependent reclassification analysis showed a trend towards incorrect lower risk reclassification using ORBIT compared to HAS-BLED. Conclusion: In this real-life contemporary cohort of AF patients treated with NOACs, the ORBIT score did not provide reclassification improvement, showing even poorer calibration compared to HAS-BLED. Our findings do not support the preferential use of

	ORBIT in NOAC-treated AF patients.
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Question	**Response**
Please confirm that this study complies with the Declaration of Helsinki (see the Instructions to Authors for more information).	Yes
Please confirm you have approval from all co-authors to submit this manuscript?	Yes
Confirm that the manuscript has been submitted solely to this journal and is not published, in press, or submitted elsewhere.	Yes
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[EHJ-QCCO-D-21-00269-R1]

REPLY TO REVIEWERS

Reviewer 1

Prediction of major bleeding by HAS-BLED and ORBIT was compared in 3018 patients receiving NOACs in EORP-AF. Both HAS-BLED and ORBIT were modestly predictive of major bleeding, but both scores were poorly calibrated. Time dependent reclassification analysis showed a trend towards incorrect lower risk reclassification using ORBIT compared to HAS-BLED. The authors concluded that the findings do not support the preferential use of ORBIT in NOAC-treated AF patients.

COMMENTS

1. Nicely presented and clinically relevant data
>>>REPLY: Many thanks for your comments.

2. Methods line 7: please provide reference for EORP-AF: Potpara TS, et al. Cohort profile: the ESC EURObservational Research Programme Atrial Fibrillation III (AF III) Registry. Eur Heart J Qual Care Clin Outcomes. 2021 May 3;7(3):229-237.
>>>REPLY: We added this (see Page 5, Lines 7-9).

3. Major bleeding defined as “intracranial hemorrhage and major extracranial hemorrhage during follow-up.” What is meant by “major extracranial haemorrhage”?
>>>REPLY: We added details on definition of major extracranial haemorrhage (see Page 7, Lines 6-8).

4. Only 20 major bleeding events during a mean of about 2 years follow-up. Why so low?
>>>REPLY: We have commented about this in Discussion section (see Page 12, Lines 16-24). Our data reflect the general low incidence of major bleeding reported in contemporary AF patients’ cohorts. Such a low incidence of major bleeding in contemporary AF patients could probably reflect both the introduction and the implementation of NOACs, as well as the general and overall improvement in AF patients’ management.

a) How confident are we that major bleeding events were recorded
>>>REPLY: The absence of a central adjudication of events represents a major limitation to the manuscript, as stated in the Limitations section. Given the important consequences related to the occurrence of a major bleeding we believe that is quite unlikely that a major bleeding would not be reported by a patient. We have discussed this in Limitations section (see Page 15, Lines 17-22).

b) What was the breakdown of major bleeding events between intracranial and extracranial haemorrhage
>>>REPLY: We added this information (see Page 9, Lines 15-16).

c) How did the low event rate compromise the ability of this study to show a significant difference between the two risk prediction models
>>>REPLY: Thank you. Compared to the derivation cohorts (e.g., EuroHeart Survey which were from a dataset of a different era, >15 years ago), we found lower rates of bleeding events. Although this may have had an influence in our ability to compare the predictive ability of the two scores, our data emphasises how both these scores may be sub-optimally calibrated in a more modern contemporary NOAC-treated AF cohort like our study (see Page 15, Lines 22-25 and Page 16, Lines 1-3).

5. Please provide mortality/stroke data. What assumptions were made about bleeding in patients who died?
>>>REPLY: We added data on ischemic stroke and all-cause death events (Page 9, Lines 19-20). As reported, the analysis of follow-up was performed according to an intention-to-treat approach. Follow-up was censored at the end of observation or at occurrence of death, whichever occurred first (see Page 7, Lines 11-13).

Comparison of HAS-BLED and ORBIT Bleeding Risk Scores in AF Patients treated with NOACs: A Report from the ESC-EHRA EORP-AF General Long-Term Registry

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ABSTRACT

Introduction: Bleeding risk assessment is recommended in guidelines for the management of atrial fibrillation (AF). HAS-BLED score was proposed prior to non-vitamin K antagonist oral anticoagulants (NOACs) and has been suggested that the ORBIT score may be superior in predicting bleeds in NOAC users. We aimed to compare the HAS-BLED and ORBIT scores in contemporary AF patients treated with NOACs.

Methods and Results: We analyzed patients enrolled in the ESC-EHRA EORP-AF General Long-Term Registry. HAS-BLED and ORBIT scores were computed based on original schemes. The primary outcome was the occurrence of Major Bleeding (MB). A total of 3018 patients (median age 70; 39.6% females) were included: median [IQR] HAS-BLED and ORBIT scores were 1 [1-2] and 1 [0-2], respectively; 356 (11.8%) patients were at high risk for MB using HAS-BLED (≥3) and 123 (4.1%) using ORBIT (≥4). Overall, 60 (2.0%) MB events were recorded, with an incidence of 1.1 per 100 patient-years.

Both HAS-BLED and ORBIT were associated with outcome, modestly predicting MB (AUC 0.653, 95% CI 0.593-0.714 and AUC 0.601, 95% CI 0.526-0.677, respectively). Calibration plots showed that both scores were poorly calibrated, particularly the ORBIT score, which showed consistent poorer calibration. Time-dependent reclassification analysis showed a trend towards incorrect lower risk reclassification using ORBIT compared to HAS-BLED.

Conclusion: In this real-life contemporary cohort of AF patients treated with NOACs, the ORBIT score did not provide reclassification improvement, showing even poorer calibration compared to HAS-BLED. Our findings do not support the preferential use of ORBIT in NOAC-treated AF patients.

Keywords: atrial fibrillation; bleeding risk; HAS-BLED; ORBIT.

INTRODUCTION

Clinical guidelines on the management of atrial fibrillation (AF) recommend the evaluation of bleeding risk factors, in order to address modifiable risk factors for mitigation, and flag up high bleeding risk patients for early review and follow-up[1–3]. Furthermore, the assessment of bleeding risk need to be re-evaluated during follow-up visits, since the risk of bleeding need to be considered as dynamic rather than static[2,4].

Among the various bleeding risk scores, the HAS-BLED score is currently recommended by most of international guidelines[1–3], on the basis of its simplicity, better predictive profile and validation across the patient pathway (untreated, antiplatelets, anticoagulants) compared to the various other bleeding scores[5,6]. The 2021 UK National Institute for Health and Care Excellence' (NICE) updated recommendation for clinical management of AF patients[7] promoted the use of the ORBIT bleeding risk score to evaluate bleeding risk in patients treated with non-vitamin K antagonist oral anticoagulants (NOACs) due to better calibration compared to other bleeding risk scores (albeit 'with very low to low quality data')[7].

As the HAS-BLED score was initially proposed in the era prior to NOACs, the aim of the present study was to formally compare the HAS-BLED and ORBIT bleeding risk scores in AF patients actually treated with NOACs in a large prospective real-world cohort of European AF patients.

METHODS

To perform this analysis, we used the dataset from the 'European Society of Cardiology - European Heart Rhythm Association' (ESC-EHRA) EURObservational Research Programme in AF (EORP-AF) General Long-Term Registry. The ESC-EHRA EORP AF General Long-Term Registry is a prospective multicentre observational registry held by the ESC and endorsed by the EHRA, with the General Long-Term Registry preceded by the EORP-AF General Pilot Registry[8–11] and followed by the ESC-EHRA EORP-AF III Registry[12], in the context of the independent observational research from the ESC. The EORP-AF General Long-Term Registry is a prospective, observational, multicentre registry established by ESC in 27 participating countries. The study enrolled 11,096 consecutive patients with AF presenting in 250 cardiology practices, in both in- and outpatient settings. The detailed description of the study design, baseline characteristics and 1-year follow-up results have been provided previously[13,14]. Briefly, all patients enrolled had AF documented within 12 months before enrolment based on objective electrocardiographic evaluation. All patients were aged ≥18 years and provided written informed consent. Enrolment was undertaken from October 2013 to September 2016, with 1-year and 2-year follow-up. Institutional review board approved the study protocol for each country and subsequently for each enrolling site, and the study was performed according to the EU Note for Guidance on Good Clinical Practice CPMP/ECH/135/95 and the Declaration of Helsinki.

For the purposes of this paper, we included in this analysis all those patients enrolled into the ESC-EHRA EORP-AF General Long-Term Registry which were prescribed with NOACs at baseline and had available data about HAS-BLED and ORBIT

bleeding scores with available follow-up information about events occurring throughout the follow-up observation.

Thromboembolic risk was defined according to CHA_2DS_2-VASc score[15]. Based on the new NICE guidelines[7], 'Low risk' was defined as a CHA_2DS_2-VASc score 0 in males and 1 in females; 'moderate risk' was defined for a CHA_2DS_2-VASc 1 in males; 'high risk' was defined as CHA_2DS_2-VASc ≥2. Symptomatic status was defined according to EHRA score[16]. Chronic AF was defined as long-standing persistent and permanent AF, while non chronic AF was defined as first detected, paroxysmal and persistent AF.

Bleeding Scores

HAS-BLED and ORBIT bleeding scores were both calculated on the basis of the original validated schemes[17,18]. In EORP-AF, the HAS-BLED score was originally calculated during baseline evaluation automatically by the electronic case report form (eCRF), based on clinical variables and medical interview. ORBIT was calculated retrospectively based on information collected into the final dataset. Clinical variables used to compile both the scores were reported in Supplementary Materials (Table S1). High bleeding risk was defined for a HAS-BLED ≥3 and for an ORBIT ≥4[17,18], respectively.

Follow-Up and Outcomes

All patients discharged alive after the baseline evaluation entered the follow-up. During follow-up all incident major adverse clinical events were recorded by each investigator and entered the eCRF at 1-year and 2-years follow-up visits. Follow-up was permitted also by telephone interview with the patient or next of kin in the case

the patients was deceased or unable to perform the interview. More details about follow-up procedures were already reported elsewhere[14].

Major bleeding was considered as the primary study outcome for this analysis. Major bleeding was defined based on occurrence of intracranial hemorrhage and major extracranial hemorrhage during follow-up. Major extracranial bleeding was defined as a bleeding event causing a drop in haemoglobin level >2 g/L, requiring blood transfusion or hospitalization occurring in any major organ system. Evaluation of bleeding outcomes was performed by each investigator and not adjudicated centrally. Follow-up analysis was performed according to an intention-to-treat approach. Follow-up was censored at the end of observation or at occurrence of death, whichever occurred first. Additionally, we reported the occurrence of ischemic stroke and all-cause death.

Statistical Analysis

Continuous variables were expressed as median and interquartile ranges. Categorical variables were expressed as counts and percentages. Difference in survival according to risk scores were assessed with Kaplan-Meier curves and Log-Rank test. Cox proportional hazard analysis were also performed to assess the occurrence of bleeding events according to both high risk categories and continuous scores. The Cox model was adjusted for female sex, EHRA score and type of AF.

For each score we also produced ROC curves and calculated the area under the curve (AUC) and 95% CI for AUC were estimated using the method by De-Long & De-Long[19]. Calibration plots were produced calculating the incidence rate (IR) of

bleeding events for each score category in our cohort, and then plotting these IRs against those reported in the derivation cohorts[17,18].

Reclassification analysis were performed with HAS-BLED as reference; integrated discrimination improvement (IDI), net reclassification improvement (NRI) and the median improvement were calculated with a time-dependent approach, using scores in continuous, and according to the method described by Pencina et al.[20], with the survIDINRI package. Decision Curve Analysis was also performed according to previously reported method[21]. Two-sided p values <0.05 were considered statistically significant. All analyses were performed with SPSS statistical software version 27.0.1 for MacOS and R 4.0.3 for Windows[22], using pROC[23], rms[24], rmda[25] and survIDINRI[26] packages.

RESULTS

From the overall cohort originally enrolled in EORP-AF, a total of 3,018 patients were included (median [IQR] age 70 [62-77] years; 1196 (39.6%) female). Median [IQR] CHA_2DS_2-VASc score was 3 [2-4], and 2180 (72.2%) were at high thromboembolic risk. Main baseline characteristics are shown in Table 1.

Distribution of bleeding scores are shown in Table 2. The mean (SD) HAS-BLED score was 1.3 (1.0) [median [IQR] score 1 [1-2]], with 356 (11.8%) at high bleeding risk. The mean ORBIT score was 1.0 (1.2) [median [IQR] 1 [0-2]], with 123 (4.1%) at high bleeding risk. Very low bleeding risk was found in 605 (20.0%) using HAS-BLED and in 1495 (49.5%) with the ORBIT score.

Incidence of Major Bleeding

Over a mean (SD) 680.79 (174.32) days of follow-up a total of 20 major bleeding events were reported (9 intracranial bleedings and 51 major extracranial haemorrhages), with an overall incidence of 1.1 per 100 patient-years. Incidence rates according to the bleeding risk scores are reported in Table 2. Major bleeding rates progressively increased according to both continuous HAS-BLED and ORBIT score points (Table 2). We also recorded a total of 54 ischemic stroke events (0.96 per 100 patient-years) and 224 all-cause death events (3.93 per 100 patient-years). Based on the HAS-BLED score, major bleeding incidence in the low bleeding risk group was 0.92 per 100 patient-years, increasing to 2.26 per 100 patient-years in the high bleeding risk group. For the ORBIT score incidence rate in low bleeding risk group was 0.94 per 100 patient-years, increasing to 4.58 per 100 patient-years in the

high risk group. Kaplan-Meier curves [Figure 1] show that for both scores, the high bleeding risk category had a greater cumulative bleeding risk than the low risk group.

Risk Scores and Major Bleeding

In the Cox regression analysis (Table 3), both the risk scores were associated with occurrence of major bleeding as continuous scores in univariate analysis and after multivariate adjustments. Similarly, the high bleeding risk category was significantly associated with the occurrence of major bleeding for both scores.

For the HAS-BLED score, those with high baseline bleeding risk (i.e., HAS-BLED ≥3) had >2-fold increase in risk (Hazard Ratio [HR] 2.26, 95% confidence interval [CI] 1.23-4.15) compared to the low bleeding risk group, after adjustment for female sex, EHRA score and type of AF (chronic vs. non-chronic). For the ORBIT score, high baseline bleeding risk (i.e., ORBIT ≥4) had >4-fold increase in risk (HR 4.62, 95% CI 2.25-9.46) compared to ORBIT score <4, after adjustment for female sex, EHRA score and type of AF.

Of the 1495 patients (49.5%) categorised as ‘very low’ bleeding risk using the ORBIT score, re-stratifying these patients by HAS-BLED score showed that 63.3% were at moderate-high bleeding risk. In this subgroup of patients (‘very low’ bleeding risk using ORBIT score), HAS-BLED score was significantly associated with risk of major bleeding (HR 1.90, 95% CI 1.26-2.85), after adjustment for female sex, EHRA score, and type of AF.

Predictive Ability, Reclassification Analysis and Calibration Plots

ROC curve analyses showed that both the scores were able to predict the occurrence of major bleeding events with a moderate ability, with HAS-BLED score reporting a numerically higher AUC (or c-index) value than the ORBIT score (AUCs 0.653, 95% CI 0.593-0.714 and AUC 0.601, 95% CI 0.526-0.677, respectively). Visual inspection of the two ROC curves seems to suggest a superiority in predicting the occurrence of major bleeding for HAS-BLED score than ORBIT score [Figure S1], but this difference was not statistically significant using the De-Long and De-Long test, p=0.216. In the cohort of 1495 (49.5%) patients with very low bleeding risk according to ORBIT score, the HAS-BLED showed a good predictive performance (AUC 0.701, 95% CI 0.614-0.788) [Figure S2].

Reclassification analyses are reported in Table 4. Projecting the risk stratification performance at 1 year of follow-up, no difference was found between the two scores. At 2 years of follow-up while a non-significant trend for lower risk reclassification capacity, in terms of NRI, with loss in median improvement for the ORBIT score compared to the HAS-BLED score. Examination of the DCA curves [Figure S3] did not show any relevant difference in net benefit by using one score or the other.

Results from the model calibration analysis comparing observed major bleeding rates in the EORP-AF registry with reported bleeding rates in the original derivation populations for HAS-BLED and ORBIT scores are shown in Figure 2. The HAS-BLED score showed good calibration for the low-risk score strata, with poor calibration in the higher bleeding risk strata. In comparison, the ORBIT score showed poorer calibration than the HAS-BLED score throughout all risk strata.

DISCUSSION

In this analysis, we found that in NOAC-treated AF patients, the use of the HAS-BLED score identified almost 12% of patients with a high risk of bleeding and 20% of patients with a very low risk of bleeding, while using the ORBIT score only identified 4% of patients at high risk of bleeding and half of the entire cohort was considered at very low risk of bleeding. Second, both the scores were significantly associated with major bleeding and predicted the event with a similarly modest capacity (c-indexes 0.60-0.65), consistent with a general performance of clinical risk scores. In the reclassification analysis, we found only a non-significant trend for poorer reclassification with the ORBIT score, while the analysis of the calibration plots showed that both the scores were not well calibrated in this cohort for the high bleeding risk strata, which was worse for the ORBIT score compared to the HAS-BLED score. These findings do not support the preferential use of ORBIT in NOAC-treated AF patients.

In this contemporary cohort of NOAC-treated AF patients, the incidence of major bleeding was low, consistent with other previous contemporary studies of AF patients management[27,28]. In an analysis derived from the GARFIELD-AF registry, the overall incidence of major bleeding was 1.31 per 100 patient-years[27]. In the follow-up of the GLORIA-AF registry phase II, the overall incidence of major bleeding was 0.97 per 100 patient-years[28]. Such a low incidence of major bleeding in contemporary AF patients could reflect both the introduction and the implementation of NOACs, as well as the general and overall improvement in AF patient management.

In AF management, the assessment of bleeding risk is essential for all the patients, both at baseline and throughout their follow-up[1–3]. The appropriate and responsible use of bleeding risk scores is really to draw attention to modifiable bleeding risk factors that can be mitigated, and to flag up the high bleeding risk patients for early review and proactive regular followup[29,30]. This strategy has been tested prospectively in the mAFA-II trial, which was a cluster randomised trial where the mAFA intervention (which used the HAS-BLED score to mitigate modifiable bleeding risks and arrange follow-up of high bleeding risk patients) was compared to usual care[31].This showed that major bleeding was lower in the intervention arm, compared to usual care; importantly, the use of OAC increased over 12 months in the intervention arm, but declined in the usual care arm[31]. Overall patients in the intervention arm showed a lower risk of adverse outcomes[32].

Many bleeding risk scores have been published thus far[33], and the HAS-BLED score has been found to be superior or performing equally compared to more complex risk scores or clinical approaches exclusively focused on modifiable bleeding risk factors[34–37]. Several systematic review and meta-analyses examining the differential ability of the various bleeding risk scores have been published, and all indicate that the HAS-BLED score provided better predictive ability, and expressing the best balance between sensitivity and specificity[5,38–40]. The ORBIT score was originally derived from a largely anticoagulated cohort from the 'Outcomes Registry for Better Informed Treatment of Atrial Fibrillation' (ORBIT-AF) study, with the aim to provide a simpler score with better predictive ability, with good calibration[18,41]. The published evidence thus far suggests that the ORBIT score does not provide any profound

advantage compared to the HAS-BLED score[34,42–44], despite a slightly superior calibration in some studies[18,41].

In terms of practical application, the ORBIT score largely focuses on non-modifiable bleeding risk factors, while the HAS-BLED score includes both modifiable and non-modifiable bleeding risk factors, which would have an impact on how patients would be categorised as low or high risk (see Figure 3 for illustrative case, also comparing with 2 other bleeding scores, ATRIA and HEMORRH$_2$AGES[33]). Indeed, categorising a patient as 'low risk' usually means 'no action' while a 'high bleeding risk' alerts from electronic medical records triggers a healthcare professional to action a follow-up plan. This is also reinforced by our exploratory analysis in the present study on the 'very low risk' patients according to ORBIT score, in which HAS-BLED was still strongly associated with occurrence of major bleeding, with a good predictive performance. Bleeding risk is also dynamic rather than static, with the risk changing with age and incident comorbidities; hence, the assessment of bleeding risk at each visit can also significantly impact the clinical course of the patients with AF[45,46].

In this context, our data reinforce and strengthen previous evidence, showing how even in a contemporary cohort of NOAC treated patients, the ORBIT score categorises a very high proportion of patients in the 'very low risk' category, not providing any gain in terms of predictive ability. While the original authors underlined the ability of ORBIT score as to be able to identify the 'real' high-risk patients, this is in contrast with the practical use of a bleeding risk score, as discussed above.

The recent update of the NICE clinical guidelines for the management of AF patients[7] recommends the use of ORBIT bleeding score in NOAC treated patients, due to the 'better calibration with this score' but 'with very low to low quality data'[7]. In the evidence review conducted by NICE (https://www.nice.org.uk/guidance/ng196/evidence/evidence-reviews-april-2021-9081923437) their recommendation was essentially based on four studies[18,41,47,48]. Two were derived from the highly selected cohorts of the NOAC phase III trials[18,41], one of which was in the specific setting of patients with a previous stroke[47] and 3 in mixed cohorts taking vitamin K antagonists and NOACs [18,41,47]. The NICE guidelines clearly state that there was no difference in terms of predictive ability, showing similar pooled AUCs for the two scores, and no difference in terms of reclassification. In this context, our data for the high bleeding risk strata also underline the poorer calibration for the ORBIT score in our AF patients taking NOACs.

Limitations

The main limitation of the current study is related to the observational nature of the registry itself. The absence of a central events adjudication with an investigator-based reporting of the adverse outcomes represents another limitation, which entails caution in interpreting the current results. Whilst an underreporting of adverse outcomes can still be possible, given the important consequences of a major bleeding event on patients' health we believe that is quite unlikely that a major bleeding event would not be reported[49,50]. Compared to the derivation cohorts we found lower rates of bleeding events; this may have influenced the comparisons of the predictive ability of the two scores. Also, we show their sub-optimally calibration in this more contemporary NOAC-treated AF cohort, being unsuitable for accurate

bleeding event rate estimation. Instead, bleeding risk scores should appropriately focus on modifiable bleeding risk factors for mitigation, and to flag up the high bleeding risk patients for review (Figure 3).

CONCLUSIONS

In this real-life contemporary cohort of AF treated with NOACs, the ORBIT score did not provide reclassification improvement or better calibration compared to HAS-BLED. Both scores were associated with a risk of MB and were sub-optimally calibrated for those in high bleeding risk strata, particularly poor with the ORBIT score. Also, the use of ORBIT score categorised a great proportion of patients into the very low risk category. Our findings do not support the preferential use of ORBIT score in NOAC-treated AF patients.

SUPPLEMENTARY MATERIALS

Supplementary Methods

Assessment of Bleeding Risk Scores

Figure S1: Bleeding Risk Scores ROC Curves for Major Bleeding Occurrence

Figure S2: HAS-BLED Score ROC Curve in ORBIT Very Low Risk Patients

Figure S3: DCA Curves for Bleeding Risk Scores

APPENDIX: EURObservational Research Programme Atrial Fibrillation (EORP-AF) Long-Term General Registry Committees and Investigators

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EORP Oversight Committee, Executive and Steering Committees (National Coordinators) of the EURObservational Research Programme (EORP) – Atrial Fibrillation General Long-Term (EORP-AF Gen LT) Registry of the European Society of Cardiology (ESC). Data collection was conducted by the EORP department by Patti-Ann McNeill as Project Officer, Viviane Missiamenou as Data Manager. Overall activities were coordinated and supervised by Doctor Aldo P. Maggioni (EORP Scientific Coordinator).

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AVAILABILITY OF DATA

All relevant data regarding the study are included in the manuscript.

REFERENCES

1. Proietti M, Lane DA, Boriani G, et al. Stroke Prevention, Evaluation of Bleeding Risk, and Anticoagulant Treatment Management in Atrial Fibrillation Contemporary International Guidelines. *Can J Cardiol* 2019; 35: 619–633.
2. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2021; 42: 373–498.
3. Lip GYH, Banerjee A, Boriani G, et al. Antithrombotic Therapy for Atrial Fibrillation: CHEST Guideline and Expert Panel Report. *Chest* 2018; 154: 1121–1201.
4. Chao T-F, Lip GYH, Lin Y-J, et al. Incident Risk Factors and Major Bleeding in Patients with Atrial Fibrillation Treated with Oral Anticoagulants: A Comparison of Baseline, Follow-up and Delta HAS-BLED Scores with an Approach Focused on Modifiable Bleeding Risk Factors. *Thromb Haemost* 2018; 118: 768–777.
5. Borre ED, Goode A, Raitz G, et al. Predicting Thromboembolic and Bleeding Event Risk in Patients with Non-Valvular Atrial Fibrillation: A Systematic Review. *Thromb Haemost* 2018; 118: 2171–2187.
6. Proietti M, Mujovic N, Potpara TS. Optimizing Stroke and Bleeding Risk Assessment in Patients with Atrial Fibrillation: A Balance of Evidence, Practicality and Precision. *Thromb Haemost* 2018; 118: 2014–2017.
7. Perry M, Kemmis Betty S, Downes N, et al. Atrial fibrillation: diagnosis and management—summary of NICE guidance. *Bmj* 2021; n1150.
8. Lip GYH, Laroche C, Dan G-A, et al. A prospective survey in European Society

of Cardiology member countries of atrial fibrillation management: baseline results of EURObservational Research Programme Atrial Fibrillation (EORP-AF) Pilot General Registry. *Europace* 2014; 16: 308–19.

9. Lip GYH, Laroche C, Ioachim PM, et al. Prognosis and treatment of atrial fibrillation patients by European cardiologists: one year follow-up of the EURObservational Research Programme-Atrial Fibrillation General Registry Pilot Phase (EORP-AF Pilot registry). *Eur Heart J* 2014; 35: 3365–76.

10. Proietti M, Laroche C, Opolski G, et al. 'Real-world' atrial fibrillation management in Europe: observations from the 2-year follow-up of the EURObservational Research Programme-Atrial Fibrillation General Registry Pilot Phase. *Europace* 2017; 19: 722–733.

11. Boriani G, Proietti M, Laroche C, et al. Changes to oral anticoagulant therapy and risk of death over a 3-year follow-up of a contemporary cohort of European patients with atrial fibrillation final report of the EURObservational Research Programme on Atrial Fibrillation (EORP-AF) pilot general r. *Int J Cardiol* 2018; 271: 68–74.

12. Potpara TS, Lip GYH, Dagres N, et al. Cohort profile: the ESC EURObservational Research Programme Atrial Fibrillation III (AF III) Registry. *Eur Hear journal Qual care Clin outcomes* 2021; 7: 229–237.

13. Boriani G, Proietti M, Laroche C, et al. Contemporary stroke prevention strategies in 11 096 European patients with atrial fibrillation: A report from the EURObservational Research Programme on Atrial Fibrillation (EORP-AF) Long-Term General Registry. *Europace* 2018; 20: 747–757.

14. Boriani G, Proietti M, Laroche C, et al. Association between antithrombotic treatment and outcomes at 1-year follow-up in patients with atrial fibrillation:

The EORP-AF General Long-Term Registry. *Europace* 2019; 21: 1013–1022.

15. Lip GYH, Nieuwlaat R, Pisters R, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest* 2010; 137: 263–72.

16. Wynn GJ, Todd DM, Webber M, et al. The European Heart Rhythm Association symptom classification for atrial fibrillation: Validation and improvement through a simple modification. *Europace* 2014; 16: 965–972.

17. Pisters R, Lane DA, Nieuwlaat R, et al. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest* 2010; 138: 1093–100.

18. O'Brien EC, Simon DN, Thomas LE, et al. The ORBIT bleeding score: A simple bedside score to assess bleeding risk in atrial fibrillation. *Eur Heart J* 2015; 36: 3258–3264.

19. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988; 44: 837–45.

20. Pencina MJ, D'Agostino RB, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med* 2008; 27: 157–72; discussion 207-12.

21. Vickers AJ, Elkin EB. Decision curve analysis: A novel method for evaluating prediction models. *Med Decis Mak* 2006; 26: 565–574.

22. R Core Team. R: A Language and Environment for Statistical Computing.

23. Robin X, Turck N, Hainard A, et al. pROC: an open-source package for R and S+ to analyze and compare ROC curves. *BMC Bioinformatics* 2011; 12: 77.

24. Harrell Jr FE. rms: Regression Modeling Strategies.

25. Brown M. rmda: Risk Model Decision Analysis.

26. Uno H, Cai T. survIDINRI: IDI and NRI for comparing competing risk prediction models with censored survival data.

27. Bassand JP, Virdone S, Badoz M, et al. Bleeding and related mortality with NOACs and VKAs in newly diagnosed atrial fibrillation: Results from the GARFIELD-AF registry. *Blood Adv* 2021; 5: 1081–1091.

28. Mazurek M, Teutsch C, Diener HC, et al. Safety and effectiveness of dabigatran at 2 years: Final outcomes from Phase II of the GLORIA-AF registry program. *Am Heart J* 2019; 218: 123–127.

29. Lip GYH, Lane DA. Bleeding risk assessment in atrial fibrillation: observations on the use and misuse of bleeding risk scores. *J Thromb Haemost* 2016; 14: 1711–1714.

30. Lip GYH, Lane DA. Assessing bleeding risk in atrial fibrillation with the HAS-BLED and ORBIT scores: Clinical application requires focus on the reversible bleeding risk factors. *Eur Heart J* 2015; 36: 3265–3267.

31. Guo Y, Lane DA, Chen Y, et al. Regular Bleeding Risk Assessment Associated with Reduction in Bleeding Outcomes: The mAFA-II Randomized Trial. *Am J Med* 2020; 133: 1195-1202.e2.

32. Guo Y, Lane DA, Wang L, et al. Mobile Health Technology to Improve Care for Patients With Atrial Fibrillation. *J Am Coll Cardiol* 2020; 75: 1523–1534.

33. Zulkifly H, Lip GYH, Lane DA. Bleeding Risk Scores in Atrial Fibrillation and Venous Thromboembolism. *Am J Cardiol* 2017; 120: 1139–1145.

34. Proietti M, Senoo K, Lane DA, et al. Major Bleeding in Patients with Non-Valvular Atrial Fibrillation: Impact of Time in Therapeutic Range on

Contemporary Bleeding Risk Scores. *Sci Rep* 2016; 6: 24376.

35. Proietti M, Rivera-Caravaca JM, Esteve-Pastor MA, et al. Predicting Bleeding Events in Anticoagulated Patients With Atrial Fibrillation: A Comparison Between the HAS-BLED and GARFIELD-AF Bleeding Scores. *J Am Heart Assoc*; 7. Epub ahead of print 18 September 2018. DOI: 10.1161/JAHA.118.009766.

36. Esteve-Pastor MA, Rivera-Caravaca JM, Roldan V, et al. Long-term bleeding risk prediction in 'real world' patients with atrial fibrillation: Comparison of the HAS-BLED and ABC-Bleeding risk scores. The Murcia Atrial Fibrillation Project. *Thromb Haemost* 2017; 117: 1848–1858.

37. Esteve-Pastor MA, Rivera-Caravaca JM, Shantsila A, et al. Assessing Bleeding Risk in Atrial Fibrillation Patients: Comparing a Bleeding Risk Score Based Only on Modifiable Bleeding Risk Factors against the HAS-BLED Score. The AMADEUS Trial. *Thromb Haemost* 2017; 117: 2261–2266.

38. Zeng J, Yu P, Cui W, et al. Comparison of HAS-BLED with other risk models for predicting the bleeding risk in anticoagulated patients with atrial fibrillation: A PRISMA-compliant article. *Medicine (Baltimore)* 2020; 99: e20782.

39. Chang G, Xie Q, Ma L, et al. Accuracy of HAS-BLED and other bleeding risk assessment tools in predicting major bleeding events in atrial fibrillation: A network meta-analysis. *J Thromb Haemost* 2020; 18: 791–801.

40. Wang C, Yu Y, Zhu W, et al. Comparing the ORBIT and HAS-BLED bleeding risk scores in anticoagulated atrial fibrillation patients: A systematic review and meta-analysis. *Oncotarget* 2017; 8: 109703–109711.

41. Proietti M, Hijazi Z, Andersson U, et al. Comparison of bleeding risk scores in patients with atrial fibrillation: insights from the RE-LY trial. *J Intern Med*; 283.

Epub ahead of print 2018. DOI: 10.1111/joim.12702.

42. Senoo K, Proietti M, Lane DA, et al. Evaluation of the HAS-BLED, ATRIA and ORBIT bleeding risk scores in atrial fibrillation patients on warfarin. *Am J Med*. Epub ahead of print 16 October 2015. DOI: 10.1016/j.amjmed.2015.10.001.

43. Senoo K, Lip GYH. Predictive abilities of the HAS-BLED and ORBIT bleeding risk scores in non-warfarin anticoagulated atrial fibrillation patients: An ancillary analysis from the AMADEUS trial. *Int J Cardiol* 2016; 221: 379–382.

44. Mori N, Sotomi Y, Hirata A, et al. External Validation of the ORBIT Bleeding Score and the HAS-BLED Score in Nonvalvular Atrial Fibrillation Patients Using Direct Oral Anticoagulants (Asian Data from the DIRECT Registry). *Am J Cardiol* 2019; 124: 1044–1048.

45. Chao T-F, Lip GYH, Lin Y-J, et al. Incident Risk Factors and Major Bleeding in Patients with Atrial Fibrillation Treated with Oral Anticoagulants: A Comparison of Baseline, Follow-up and Delta HAS-BLED Scores with an Approach Focused on Modifiable Bleeding Risk Factors. *Thromb Haemost* 2018; 118: 768–777.

46. Fabritz L, Crijns HJGM, Guasch E, et al. Dynamic risk assessment to improve quality of care in patients with atrial fibrillation: The 7th AFNET/EHRA Consensus Conference. *Europace* 2021; 23: 329–344.

47. Hilkens NA, Algra A, Greving JP. Predicting major bleeding in ischemic stroke patients with atrial fibrillation. *Stroke* 2017; 48: 3142–3144.

48. Lip GYH, Skjøth F, Nielsen PB, et al. The HAS-BLED, ATRIA, and ORBIT Bleeding Scores in Atrial Fibrillation Patients Using Non-Vitamin K Antagonist Oral Anticoagulants. *Am J Med* 2018; 131: 574.e13-574.e27.

49. Gómez-Outes A, Lagunar-Ruíz J, Terleira-Fernández AI, et al. Causes of

Death in Anticoagulated Patients With Atrial Fibrillation. *J Am Coll Cardiol* 2016; 68: 2508–2521.

50. Steinberg BA, Simon DN, Thomas L, et al. Management of Major Bleeding in Patients With Atrial Fibrillation Treated With Non-Vitamin K Antagonist Oral Anticoagulants Compared With Warfarin in Clinical Practice (from Phase II of the Outcomes Registry for Better Informed Treatment of Atrial Fibrill. *Am J Cardiol* 2017; 119: 1590–1595.

FIGURES LEGENDS

Figure 1: Kaplan-Meier Curves for Bleeding Risk Scores

Legend: HAS-BLED) Log-Rank= 9.044, p=0.003; ORBIT) Log-Rank= 22.932, p<0.001.

Figure 2: Calibration Curves for Bleeding Risk Scores in EORP-AF Cohort

Legend: EORP-AF= EURObservational Research Programme in Atrial Fibrillation.

Figure 3: Illustrative Case for Baseline Bleeding Risk Evaluation in AF Patients

Legend: AF= Atrial Fibrillation; BP= Blood Pressure; ESC= European Society of Cardiology; NSAIDs= Non-Steroidal Anti-Inflammatory Drugs; OAC= Oral Anticoagulant.

Table 1: Baseline Characteristics of Patients Included in the Analysis

	EORP-AF LT General Registry N= 3018
Age, *years* median [IQR]	70 [62-77]
Female Sex, n (%)	1196 (39.6)
BMI, *kg/m²* median [IQR]	27.8 [25.0-31.5]
CrCl, *mL/min* median [IQR]	77.6 [58.3-100.0]
SBP, *mmHg* median [IQR]	130 [120-142]
DBP, *mmHg* median [IQR]	80 [70-88]
Chronic AF, n (%)	684 (22.7)
Heart Failure, n (%)	938 (31.1)
Hypertension, n (%)	1809 (59.9)
Diabetes Mellitus, n (%)	632 (20.9)
CAD, n (%)	642 (21.3)
PAD, n (%)	202 (607)
Stroke/TIA, n (%)	277 (9.2)
Previous Bleeding, n (%)	159 (5.3)
Liver Disease, n (%)	49 (1.6)
CKD, n (%)	209 (10.2)
CHA_2DS_2-VASc, median [IQR]	3 [2-4]

Legend: AF= Atrial Fibrillation; BMI= Body Mass Index; CAD= Coronary Artery Disease; CKD= Chronic Kidney Disease; CrCl= Creatinine Clearance; DBP= Diastolic Blood Pressure; EORP-AF= EURObservational Research Programme in Atrial Fibrillation;n iii909k988iiì,' IQR= Interquartile Range; LT= Long-Term; PAD= Peripheral Artery Disease; SBP= Systolic Blood Pressure; TIA= Transient Ischemic Attack.

Table 2: Bleeding Scores Distribution and Incidence of Major Bleeding

	HAS-BLED		ORBIT	
Mean (SD)	1.3 (1.0)		1.0 (1.2)	
Median [IQR]	1 [1-2]		1 [0-2]	
High Bleeding Risk, N (%)	356 (11.8%)		123 (4.1%)	
	N (%)	**MB (N, [IR])**	**N (%)**	**MB (N, [IR])**
0	605 (20.0)	2 (0.2)	1495 (49.5)	23 (0.8)
1	1199 (39.7)	20 (0.9)	732 (24.3)	10 (0.7)
2	858 (28.4)	24 (1.5)	357 (11.8)	10 (1.5)
3	290 (9.6)	9 (1.7)	311 (10.3)	8 (1.5)
4	59 (2.0)	4 (4.2)	80 (2.7)	4 (3.0)
5	7 (0.2)	1 (11.6)	38 (1.3)	5 (9.5)
6	-	-	5 (0.2)	0 (0)
7	-	-	-	-
8	-	-	-	-
9	-	-	-	-

Legend: IQR= Interquartile Range; IR= Incidence Rate; MB= Major Bleeding.

Table 3: Association between Bleeding Risk Scores and Risk of Major Bleeding Occurrence

	Univariate Analysis			Multivariate Analysis*		
	HR	**95% CI**	**p**	**HR**	**95% CI**	**p**
HAS-BLED						
Continuous Score	1.78	1.41-2.25	<0.001	1.74	1.37-2.21	<0.001
≥3 *(vs. <3)*	2.43	1.34-4.42	0.004	2.26	1.23-4.15	0.008
ORBIT						
Continuous Score	1.43	1.21-1.69	<0.001	1.42	1.20-1.68	<0.001
≥4 *(vs. <4)*	4.79	2.36-9.73	<0.001	4.62	2.25-9.46	<0.001

Legend: *adjusted for female sex, EHRA score and type of AF; AF= Atrial Fibrillation; CI= Confidence Interval; EHRA= European Heart Rhythm Association; HR= Hazard Ratio.

Table 4: Reclassification Analysis for Bleeding Risk Scores about Major Bleeding Occurrence

ORBIT vs. HAS-BLED	**IDI (95% CI)**	**p**	**NRI (95% CI)**	**p**	**MI (95% CI)**	**p**
1 year FU	-0.001	0.757	-0.069	0.465	-0.002	0.120
	(-0.009 / 0.009)		(-0.193 / 0.138)		(-0.004 / 0.002)	
2 years FU	-0.002	0.691	-0.117	0.093	-0.002	0.093
	(-0.018 / 0.015)		(-0.301 / 0.018)		(-0.013 / 0.001)	

Legend: CI= Confidence Interval; FU= Follow-Up; IDI= Integrated Discrimination Improvement; MI= Median Improvement; NRI= Net Reclassification Index.

Comparison of HAS-BLED and ORBIT Bleeding Risk Scores in AF Patients treated with NOACs: A Report from the ESC-EHRA EORP-AF General Long-Term Registry

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ABSTRACT

Introduction: Bleeding risk assessment is recommended in guidelines for the management of atrial fibrillation (AF). HAS-BLED score was proposed prior to non-vitamin K antagonist oral anticoagulants (NOACs) and has been suggested that the ORBIT score may be superior in predicting bleeds in NOAC users. We aimed to compare the HAS-BLED and ORBIT scores in contemporary AF patients treated with NOACs.

Methods and Results: We analyzed patients enrolled in the ESC-EHRA EORP-AF General Long-Term Registry. HAS-BLED and ORBIT scores were computed based on original schemes. The primary outcome was the occurrence of Major Bleeding (MB). A total of 3018 patients (median age 70; 39.6% females) were included: median [IQR] HAS-BLED and ORBIT scores were 1 [1-2] and 1 [0-2], respectively; 356 (11.8%) patients were at high risk for MB using HAS-BLED (≥3) and 123 (4.1%) using ORBIT (≥4). Overall, 60 (2.0%) MB events were recorded, with an incidence of 1.1 per 100 patient-years.

Both HAS-BLED and ORBIT were associated with outcome, modestly predicting MB (AUC 0.653, 95% CI 0.593-0.714 and AUC 0.601, 95% CI 0.526-0.677, respectively). Calibration plots showed that both scores were poorly calibrated, particularly the ORBIT score, which showed consistent poorer calibration. Time-dependent reclassification analysis showed a trend towards incorrect lower risk reclassification using ORBIT compared to HAS-BLED.

Conclusion: In this real-life contemporary cohort of AF patients treated with NOACs, the ORBIT score did not provide reclassification improvement, showing even poorer calibration compared to HAS-BLED. Our findings do not support the preferential use of ORBIT in NOAC-treated AF patients.

Keywords: atrial fibrillation; bleeding risk; HAS-BLED; ORBIT.

INTRODUCTION

Clinical guidelines on the management of atrial fibrillation (AF) recommend the evaluation of bleeding risk factors, in order to address modifiable risk factors for mitigation, and flag up high bleeding risk patients for early review and follow-up[1–3]. Furthermore, the assessment of bleeding risk need to be re-evaluated during follow-up visits, since the risk of bleeding need to be considered as dynamic rather than static[2,4].

Among the various bleeding risk scores, the HAS-BLED score is currently recommended by most of international guidelines[1–3], on the basis of its simplicity, better predictive profile and validation across the patient pathway (untreated, antiplatelets, anticoagulants) compared to the various other bleeding scores[5,6]. The 2021 UK National Institute for Health and Care Excellence' (NICE) updated recommendation for clinical management of AF patients[7] promoted the use of the ORBIT bleeding risk score to evaluate bleeding risk in patients treated with non-vitamin K antagonist oral anticoagulants (NOACs) due to better calibration compared to other bleeding risk scores (albeit 'with very low to low quality data')[7].

As the HAS-BLED score was initially proposed in the era prior to NOACs, the aim of the present study was to formally compare the HAS-BLED and ORBIT bleeding risk scores in AF patients actually treated with NOACs in a large prospective real-world cohort of European AF patients.

METHODS

To perform this analysis, we used the dataset from the 'European Society of Cardiology - European Heart Rhythm Association' (ESC-EHRA) EURObservational Research Programme in AF (EORP-AF) General Long-Term Registry. The ESC-EHRA EORP AF General Long-Term Registry is a prospective multicentre observational registry held by the ESC and endorsed by the EHRA, with the General Long-Term Registry preceded by the EORP-AF General Pilot Registry[8–11] and followed by the ESC-EHRA EORP-AF III Registry[12], in the context of the independent observational research from the ESC. The EORP-AF General Long-Term Registry is a prospective, observational, multicentre registry established by ESC in 27 participating countries. The study enrolled 11,096 consecutive patients with AF presenting in 250 cardiology practices, in both in- and outpatient settings. The detailed description of the study design, baseline characteristics and 1-year follow-up results have been provided previously[13,14]. Briefly, all patients enrolled had AF documented within 12 months before enrolment based on objective electrocardiographic evaluation. All patients were aged ≥18 years and provided written informed consent. Enrolment was undertaken from October 2013 to September 2016, with 1-year and 2-year follow-up. Institutional review board approved the study protocol for each country and subsequently for each enrolling site, and the study was performed according to the EU Note for Guidance on Good Clinical Practice CPMP/ECH/135/95 and the Declaration of Helsinki.

For the purposes of this paper, we included in this analysis all those patients enrolled into the ESC-EHRA EORP-AF General Long-Term Registry which were prescribed with NOACs at baseline and had available data about HAS-BLED and ORBIT

bleeding scores with available follow-up information about events occurring throughout the follow-up observation.

Thromboembolic risk was defined according to CHA_2DS_2-VASc score[15]. Based on the new NICE guidelines[7], 'Low risk' was defined as a CHA_2DS_2-VASc score 0 in males and 1 in females; 'moderate risk' was defined for a CHA_2DS_2-VASc 1 in males; 'high risk' was defined as CHA_2DS_2-VASc ≥2. Symptomatic status was defined according to EHRA score[16]. Chronic AF was defined as long-standing persistent and permanent AF, while non chronic AF was defined as first detected, paroxysmal and persistent AF.

Bleeding Scores

HAS-BLED and ORBIT bleeding scores were both calculated on the basis of the original validated schemes[17,18]. In EORP-AF, the HAS-BLED score was originally calculated during baseline evaluation automatically by the electronic case report form (eCRF), based on clinical variables and medical interview. ORBIT was calculated retrospectively based on information collected into the final dataset. Clinical variables used to compile both the scores were reported in Supplementary Materials (Table S1). High bleeding risk was defined for a HAS-BLED ≥3 and for an ORBIT ≥4[17,18], respectively.

Follow-Up and Outcomes

All patients discharged alive after the baseline evaluation entered the follow-up. During follow-up all incident major adverse clinical events were recorded by each investigator and entered the eCRF at 1-year and 2-years follow-up visits. Follow-up was permitted also by telephone interview with the patient or next of kin in the case

the patients was deceased or unable to perform the interview. More details about follow-up procedures were already reported elsewhere[14].

Major bleeding was considered as the primary study outcome for this analysis. Major bleeding was defined based on occurrence of intracranial hemorrhage and major extracranial hemorrhage during follow-up. Major extracranial bleeding was defined as a bleeding event causing a drop in haemoglobin level >2 g/L, requiring blood transfusion or hospitalization occurring in any major organ system. Evaluation of bleeding outcomes was performed by each investigator and not adjudicated centrally. Follow-up analysis was performed according to an intention-to-treat approach. Follow-up was censored at the end of observation or at occurrence of death, whichever occurred first. Additionally, we reported the occurrence of ischemic stroke and all-cause death.

Statistical Analysis

Continuous variables were expressed as median and interquartile ranges. Categorical variables were expressed as counts and percentages. Difference in survival according to risk scores were assessed with Kaplan-Meier curves and Log-Rank test. Cox proportional hazard analysis were also performed to assess the occurrence of bleeding events according to both high risk categories and continuous scores. The Cox model was adjusted for female sex, EHRA score and type of AF.

For each score we also produced ROC curves and calculated the area under the curve (AUC) and 95% CI for AUC were estimated using the method by De-Long & De-Long[19]. Calibration plots were produced calculating the incidence rate (IR) of

bleeding events for each score category in our cohort, and then plotting these IRs against those reported in the derivation cohorts[17,18].

Reclassification analysis were performed with HAS-BLED as reference; integrated discrimination improvement (IDI), net reclassification improvement (NRI) and the median improvement were calculated with a time-dependent approach, using scores in continuous, and according to the method described by Pencina et al.[20], with the survIDINRI package. Decision Curve Analysis was also performed according to previously reported method[21]. Two-sided p values <0.05 were considered statistically significant. All analyses were performed with SPSS statistical software version 27.0.1 for MacOS and R 4.0.3 for Windows[22], using pROC[23], rms[24], rmda[25] and survIDINRI[26] packages.

RESULTS

From the overall cohort originally enrolled in EORP-AF, a total of 3,018 patients were included (median [IQR] age 70 [62-77] years; 1196 (39.6%) female). Median [IQR] CHA_2DS_2-VASc score was 3 [2-4], and 2180 (72.2%) were at high thromboembolic risk. Main baseline characteristics are shown in Table 1.

Distribution of bleeding scores are shown in Table 2. The mean (SD) HAS-BLED score was 1.3 (1.0) [median [IQR] score 1 [1-2]], with 356 (11.8%) at high bleeding risk. The mean ORBIT score was 1.0 (1.2) [median [IQR] 1 [0-2]], with 123 (4.1%) at high bleeding risk. Very low bleeding risk was found in 605 (20.0%) using HAS-BLED and in 1495 (49.5%) with the ORBIT score.

Incidence of Major Bleeding

Over a mean (SD) 680.79 (174.32) days of follow-up a total of 20 major bleeding events were reported (9 intracranial bleedings and 51 major extracranial haemorrhages), with an overall incidence of 1.1 per 100 patient-years. Incidence rates according to the bleeding risk scores are reported in Table 2. Major bleeding rates progressively increased according to both continuous HAS-BLED and ORBIT score points (Table 2). We also recorded a total of 54 ischemic stroke events (0.96 per 100 patient-years) and 224 all-cause death events (3.93 per 100 patient-years). Based on the HAS-BLED score, major bleeding incidence in the low bleeding risk group was 0.92 per 100 patient-years, increasing to 2.26 per 100 patient-years in the high bleeding risk group. For the ORBIT score incidence rate in low bleeding risk group was 0.94 per 100 patient-years, increasing to 4.58 per 100 patient-years in the

high risk group. Kaplan-Meier curves [Figure 1] show that for both scores, the high bleeding risk category had a greater cumulative bleeding risk than the low risk group.

Risk Scores and Major Bleeding

In the Cox regression analysis (Table 3), both the risk scores were associated with occurrence of major bleeding as continuous scores in univariate analysis and after multivariate adjustments. Similarly, the high bleeding risk category was significantly associated with the occurrence of major bleeding for both scores.

For the HAS-BLED score, those with high baseline bleeding risk (i.e., HAS-BLED ≥3) had >2-fold increase in risk (Hazard Ratio [HR] 2.26, 95% confidence interval [CI] 1.23-4.15) compared to the low bleeding risk group, after adjustment for female sex, EHRA score and type of AF (chronic vs. non-chronic). For the ORBIT score, high baseline bleeding risk (i.e., ORBIT ≥4) had >4-fold increase in risk (HR 4.62, 95% CI 2.25-9.46) compared to ORBIT score <4, after adjustment for female sex, EHRA score and type of AF.

Of the 1495 patients (49.5%) categorised as ‘very low’ bleeding risk using the ORBIT score, re-stratifying these patients by HAS-BLED score showed that 63.3% were at moderate-high bleeding risk. In this subgroup of patients (‘very low’ bleeding risk using ORBIT score), HAS-BLED score was significantly associated with risk of major bleeding (HR 1.90, 95% CI 1.26-2.85), after adjustment for female sex, EHRA score, and type of AF.

Predictive Ability, Reclassification Analysis and Calibration Plots

ROC curve analyses showed that both the scores were able to predict the occurrence of major bleeding events with a moderate ability, with HAS-BLED score reporting a numerically higher AUC (or c-index) value than the ORBIT score (AUCs 0.653, 95% CI 0.593-0.714 and AUC 0.601, 95% CI 0.526-0.677, respectively). Visual inspection of the two ROC curves seems to suggest a superiority in predicting the occurrence of major bleeding for HAS-BLED score than ORBIT score [Figure S1], but this difference was not statistically significant using the De-Long and De-Long test, p=0.216. In the cohort of 1495 (49.5%) patients with very low bleeding risk according to ORBIT score, the HAS-BLED showed a good predictive performance (AUC 0.701, 95% CI 0.614-0.788) [Figure S2].

Reclassification analyses are reported in Table 4. Projecting the risk stratification performance at 1 year of follow-up, no difference was found between the two scores. At 2 years of follow-up while a non-significant trend for lower risk reclassification capacity, in terms of NRI, with loss in median improvement for the ORBIT score compared to the HAS-BLED score. Examination of the DCA curves [Figure S3] did not show any relevant difference in net benefit by using one score or the other.

Results from the model calibration analysis comparing observed major bleeding rates in the EORP-AF registry with reported bleeding rates in the original derivation populations for HAS-BLED and ORBIT scores are shown in Figure 2. The HAS-BLED score showed good calibration for the low-risk score strata, with poor calibration in the higher bleeding risk strata. In comparison, the ORBIT score showed poorer calibration than the HAS-BLED score throughout all risk strata.

DISCUSSION

In this analysis, we found that in NOAC-treated AF patients, the use of the HAS-BLED score identified almost 12% of patients with a high risk of bleeding and 20% of patients with a very low risk of bleeding, while using the ORBIT score only identified 4% of patients at high risk of bleeding and half of the entire cohort was considered at very low risk of bleeding. Second, both the scores were significantly associated with major bleeding and predicted the event with a similarly modest capacity (c-indexes 0.60-0.65), consistent with a general performance of clinical risk scores. In the reclassification analysis, we found only a non-significant trend for poorer reclassification with the ORBIT score, while the analysis of the calibration plots showed that both the scores were not well calibrated in this cohort for the high bleeding risk strata, which was worse for the ORBIT score compared to the HAS-BLED score. These findings do not support the preferential use of ORBIT in NOAC-treated AF patients.

In this contemporary cohort of NOAC-treated AF patients, the incidence of major bleeding was low, consistent with other previous contemporary studies of AF patients management[27,28]. In an analysis derived from the GARFIELD-AF registry, the overall incidence of major bleeding was 1.31 per 100 patient-years[27]. In the follow-up of the GLORIA-AF registry phase II, the overall incidence of major bleeding was 0.97 per 100 patient-years[28]. Such a low incidence of major bleeding in contemporary AF patients could reflect both the introduction and the implementation of NOACs, as well as the general and overall improvement in AF patient management.

In AF management, the assessment of bleeding risk is essential for all the patients, both at baseline and throughout their follow-up[1–3]. The appropriate and responsible use of bleeding risk scores is really to draw attention to modifiable bleeding risk factors that can be mitigated, and to flag up the high bleeding risk patients for early review and proactive regular followup[29,30]. This strategy has been tested prospectively in the mAFA-II trial, which was a cluster randomised trial where the mAFA intervention (which used the HAS-BLED score to mitigate modifiable bleeding risks and arrange follow-up of high bleeding risk patients) was compared to usual care[31].This showed that major bleeding was lower in the intervention arm, compared to usual care; importantly, the use of OAC increased over 12 months in the intervention arm, but declined in the usual care arm[31]. Overall patients in the intervention arm showed a lower risk of adverse outcomes[32].

Many bleeding risk scores have been published thus far[33], and the HAS-BLED score has been found to be superior or performing equally compared to more complex risk scores or clinical approaches exclusively focused on modifiable bleeding risk factors[34–37]. Several systematic review and meta-analyses examining the differential ability of the various bleeding risk scores have been published, and all indicate that the HAS-BLED score provided better predictive ability, and expressing the best balance between sensitivity and specificity[5,38–40]. The ORBIT score was originally derived from a largely anticoagulated cohort from the ‘Outcomes Registry for Better Informed Treatment of Atrial Fibrillation’ (ORBIT-AF) study, with the aim to provide a simpler score with better predictive ability, with good calibration[18,41]. The published evidence thus far suggests that the ORBIT score does not provide any profound

advantage compared to the HAS-BLED score[34,42–44], despite a slightly superior calibration in some studies[18,41].

In terms of practical application, the ORBIT score largely focuses on non-modifiable bleeding risk factors, while the HAS-BLED score includes both modifiable and non-modifiable bleeding risk factors, which would have an impact on how patients would be categorised as low or high risk (see Figure 3 for illustrative case, also comparing with 2 other bleeding scores, ATRIA and HEMORRH$_2$AGES[33]). Indeed, categorising a patient as 'low risk' usually means 'no action' while a 'high bleeding risk' alerts from electronic medical records triggers a healthcare professional to action a follow-up plan. This is also reinforced by our exploratory analysis in the present study on the 'very low risk' patients according to ORBIT score, in which HAS-BLED was still strongly associated with occurrence of major bleeding, with a good predictive performance. Bleeding risk is also dynamic rather than static, with the risk changing with age and incident comorbidities; hence, the assessment of bleeding risk at each visit can also significantly impact the clinical course of the patients with AF[45,46].

In this context, our data reinforce and strengthen previous evidence, showing how even in a contemporary cohort of NOAC treated patients, the ORBIT score categorises a very high proportion of patients in the 'very low risk' category, not providing any gain in terms of predictive ability. While the original authors underlined the ability of ORBIT score as to be able to identify the 'real' high-risk patients, this is in contrast with the practical use of a bleeding risk score, as discussed above.

The recent update of the NICE clinical guidelines for the management of AF patients[7] recommends the use of ORBIT bleeding score in NOAC treated patients, due to the 'better calibration with this score' but 'with very low to low quality data'[7]. In the evidence review conducted by NICE (https://www.nice.org.uk/guidance/ng196/evidence/evidence-reviews-april-2021-9081923437) their recommendation was essentially based on four studies[18,41,47,48]. Two were derived from the highly selected cohorts of the NOAC phase III trials[18,41], one of which was in the specific setting of patients with a previous stroke[47] and 3 in mixed cohorts taking vitamin K antagonists and NOACs [18,41,47]. The NICE guidelines clearly state that there was no difference in terms of predictive ability, showing similar pooled AUCs for the two scores, and no difference in terms of reclassification. In this context, our data for the high bleeding risk strata also underline the poorer calibration for the ORBIT score in our AF patients taking NOACs.

Limitations

The main limitation of the current study is related to the observational nature of the registry itself. The absence of a central events adjudication with an investigator-based reporting of the adverse outcomes represents another limitation, which entails caution in interpreting the current results. Whilst an underreporting of adverse outcomes can still be possible, given the important consequences of a major bleeding event on patients' health we believe that is quite unlikely that a major bleeding event would not be reported[49,50]. Compared to the derivation cohorts we found lower rates of bleeding events; this may have influenced the comparisons of the predictive ability of the two scores. Also, we show their sub-optimally calibration in this more contemporary NOAC-treated AF cohort, being unsuitable for accurate

bleeding event rate estimation. Instead, bleeding risk scores should appropriately focus on modifiable bleeding risk factors for mitigation, and to flag up the high bleeding risk patients for review (Figure 3).

CONCLUSIONS

In this real-life contemporary cohort of AF treated with NOACs, the ORBIT score did not provide reclassification improvement or better calibration compared to HAS-BLED. Both scores were associated with a risk of MB and were sub-optimally calibrated for those in high bleeding risk strata, particularly poor with the ORBIT score. Also, the use of ORBIT score categorised a great proportion of patients into the very low risk category. Our findings do not support the preferential use of ORBIT score in NOAC-treated AF patients.

SUPPLEMENTARY MATERIALS

Supplementary Methods

Assessment of Bleeding Risk Scores

Figure S1: Bleeding Risk Scores ROC Curves for Major Bleeding Occurrence

Figure S2: HAS-BLED Score ROC Curve in ORBIT Very Low Risk Patients

Figure S3: DCA Curves for Bleeding Risk Scores

APPENDIX: EURObservational Research Programme Atrial Fibrillation (EORP-AF) Long-Term General Registry Committees and Investigators

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GB received small speaker's fees from Medtronic, Boston, Boehringer Ingelheim and Bayer; **GYHL** has been consultant and speaker for BMS/Pfizer, Boehringer Ingelheim and Daiichi-Sankyo. No fees are directly received personally. All other authors have nothing to declare**.**

AVAILABILITY OF DATA

All relevant data regarding the study are included in the manuscript.

REFERENCES

1. Proietti M, Lane DA, Boriani G, et al. Stroke Prevention, Evaluation of Bleeding Risk, and Anticoagulant Treatment Management in Atrial Fibrillation Contemporary International Guidelines. *Can J Cardiol* 2019; 35: 619–633.
2. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2021; 42: 373–498.
3. Lip GYH, Banerjee A, Boriani G, et al. Antithrombotic Therapy for Atrial Fibrillation: CHEST Guideline and Expert Panel Report. *Chest* 2018; 154: 1121–1201.
4. Chao T-F, Lip GYH, Lin Y-J, et al. Incident Risk Factors and Major Bleeding in Patients with Atrial Fibrillation Treated with Oral Anticoagulants: A Comparison of Baseline, Follow-up and Delta HAS-BLED Scores with an Approach Focused on Modifiable Bleeding Risk Factors. *Thromb Haemost* 2018; 118: 768–777.
5. Borre ED, Goode A, Raitz G, et al. Predicting Thromboembolic and Bleeding Event Risk in Patients with Non-Valvular Atrial Fibrillation: A Systematic Review. *Thromb Haemost* 2018; 118: 2171–2187.
6. Proietti M, Mujovic N, Potpara TS. Optimizing Stroke and Bleeding Risk Assessment in Patients with Atrial Fibrillation: A Balance of Evidence, Practicality and Precision. *Thromb Haemost* 2018; 118: 2014–2017.
7. Perry M, Kemmis Betty S, Downes N, et al. Atrial fibrillation: diagnosis and management—summary of NICE guidance. *Bmj* 2021; n1150.
8. Lip GYH, Laroche C, Dan G-A, et al. A prospective survey in European Society

of Cardiology member countries of atrial fibrillation management: baseline results of EURObservational Research Programme Atrial Fibrillation (EORP-AF) Pilot General Registry. *Europace* 2014; 16: 308–19.

9. Lip GYH, Laroche C, Ioachim PM, et al. Prognosis and treatment of atrial fibrillation patients by European cardiologists: one year follow-up of the EURObservational Research Programme-Atrial Fibrillation General Registry Pilot Phase (EORP-AF Pilot registry). *Eur Heart J* 2014; 35: 3365–76.

10. Proietti M, Laroche C, Opolski G, et al. 'Real-world' atrial fibrillation management in Europe: observations from the 2-year follow-up of the EURObservational Research Programme-Atrial Fibrillation General Registry Pilot Phase. *Europace* 2017; 19: 722–733.

11. Boriani G, Proietti M, Laroche C, et al. Changes to oral anticoagulant therapy and risk of death over a 3-year follow-up of a contemporary cohort of European patients with atrial fibrillation final report of the EURObservational Research Programme on Atrial Fibrillation (EORP-AF) pilot general r. *Int J Cardiol* 2018; 271: 68–74.

12. Potpara TS, Lip GYH, Dagres N, et al. Cohort profile: the ESC EURObservational Research Programme Atrial Fibrillation III (AF III) Registry. *Eur Hear journal Qual care Clin outcomes* 2021; 7: 229–237.

13. Boriani G, Proietti M, Laroche C, et al. Contemporary stroke prevention strategies in 11 096 European patients with atrial fibrillation: A report from the EURObservational Research Programme on Atrial Fibrillation (EORP-AF) Long-Term General Registry. *Europace* 2018; 20: 747–757.

14. Boriani G, Proietti M, Laroche C, et al. Association between antithrombotic treatment and outcomes at 1-year follow-up in patients with atrial fibrillation:

The EORP-AF General Long-Term Registry. *Europace* 2019; 21: 1013–1022.

15. Lip GYH, Nieuwlaat R, Pisters R, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest* 2010; 137: 263–72.

16. Wynn GJ, Todd DM, Webber M, et al. The European Heart Rhythm Association symptom classification for atrial fibrillation: Validation and improvement through a simple modification. *Europace* 2014; 16: 965–972.

17. Pisters R, Lane DA, Nieuwlaat R, et al. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest* 2010; 138: 1093–100.

18. O'Brien EC, Simon DN, Thomas LE, et al. The ORBIT bleeding score: A simple bedside score to assess bleeding risk in atrial fibrillation. *Eur Heart J* 2015; 36: 3258–3264.

19. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988; 44: 837–45.

20. Pencina MJ, D'Agostino RB, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med* 2008; 27: 157–72; discussion 207-12.

21. Vickers AJ, Elkin EB. Decision curve analysis: A novel method for evaluating prediction models. *Med Decis Mak* 2006; 26: 565–574.

22. R Core Team. R: A Language and Environment for Statistical Computing.

23. Robin X, Turck N, Hainard A, et al. pROC: an open-source package for R and S+ to analyze and compare ROC curves. *BMC Bioinformatics* 2011; 12: 77.

24. Harrell Jr FE. rms: Regression Modeling Strategies.
25. Brown M. rmda: Risk Model Decision Analysis.
26. Uno H, Cai T. survIDINRI: IDI and NRI for comparing competing risk prediction models with censored survival data.
27. Bassand JP, Virdone S, Badoz M, et al. Bleeding and related mortality with NOACs and VKAs in newly diagnosed atrial fibrillation: Results from the GARFIELD-AF registry. *Blood Adv* 2021; 5: 1081–1091.
28. Mazurek M, Teutsch C, Diener HC, et al. Safety and effectiveness of dabigatran at 2 years: Final outcomes from Phase II of the GLORIA-AF registry program. *Am Heart J* 2019; 218: 123–127.
29. Lip GYH, Lane DA. Bleeding risk assessment in atrial fibrillation: observations on the use and misuse of bleeding risk scores. *J Thromb Haemost* 2016; 14: 1711–1714.
30. Lip GYH, Lane DA. Assessing bleeding risk in atrial fibrillation with the HAS-BLED and ORBIT scores: Clinical application requires focus on the reversible bleeding risk factors. *Eur Heart J* 2015; 36: 3265–3267.
31. Guo Y, Lane DA, Chen Y, et al. Regular Bleeding Risk Assessment Associated with Reduction in Bleeding Outcomes: The mAFA-II Randomized Trial. *Am J Med* 2020; 133: 1195-1202.e2.
32. Guo Y, Lane DA, Wang L, et al. Mobile Health Technology to Improve Care for Patients With Atrial Fibrillation. *J Am Coll Cardiol* 2020; 75: 1523–1534.
33. Zulkifly H, Lip GYH, Lane DA. Bleeding Risk Scores in Atrial Fibrillation and Venous Thromboembolism. *Am J Cardiol* 2017; 120: 1139–1145.
34. Proietti M, Senoo K, Lane DA, et al. Major Bleeding in Patients with Non-Valvular Atrial Fibrillation: Impact of Time in Therapeutic Range on

Contemporary Bleeding Risk Scores. *Sci Rep* 2016; 6: 24376.

35. Proietti M, Rivera-Caravaca JM, Esteve-Pastor MA, et al. Predicting Bleeding Events in Anticoagulated Patients With Atrial Fibrillation: A Comparison Between the HAS-BLED and GARFIELD-AF Bleeding Scores. *J Am Heart Assoc*; 7. Epub ahead of print 18 September 2018. DOI: 10.1161/JAHA.118.009766.

36. Esteve-Pastor MA, Rivera-Caravaca JM, Roldan V, et al. Long-term bleeding risk prediction in 'real world' patients with atrial fibrillation: Comparison of the HAS-BLED and ABC-Bleeding risk scores. The Murcia Atrial Fibrillation Project. *Thromb Haemost* 2017; 117: 1848–1858.

37. Esteve-Pastor MA, Rivera-Caravaca JM, Shantsila A, et al. Assessing Bleeding Risk in Atrial Fibrillation Patients: Comparing a Bleeding Risk Score Based Only on Modifiable Bleeding Risk Factors against the HAS-BLED Score. The AMADEUS Trial. *Thromb Haemost* 2017; 117: 2261–2266.

38. Zeng J, Yu P, Cui W, et al. Comparison of HAS-BLED with other risk models for predicting the bleeding risk in anticoagulated patients with atrial fibrillation: A PRISMA-compliant article. *Medicine (Baltimore)* 2020; 99: e20782.

39. Chang G, Xie Q, Ma L, et al. Accuracy of HAS-BLED and other bleeding risk assessment tools in predicting major bleeding events in atrial fibrillation: A network meta-analysis. *J Thromb Haemost* 2020; 18: 791–801.

40. Wang C, Yu Y, Zhu W, et al. Comparing the ORBIT and HAS-BLED bleeding risk scores in anticoagulated atrial fibrillation patients: A systematic review and meta-analysis. *Oncotarget* 2017; 8: 109703–109711.

41. Proietti M, Hijazi Z, Andersson U, et al. Comparison of bleeding risk scores in patients with atrial fibrillation: insights from the RE-LY trial. *J Intern Med*; 283.

Epub ahead of print 2018. DOI: 10.1111/joim.12702.

42. Senoo K, Proietti M, Lane DA, et al. Evaluation of the HAS-BLED, ATRIA and ORBIT bleeding risk scores in atrial fibrillation patients on warfarin. *Am J Med*. Epub ahead of print 16 October 2015. DOI: 10.1016/j.amjmed.2015.10.001.

43. Senoo K, Lip GYH. Predictive abilities of the HAS-BLED and ORBIT bleeding risk scores in non-warfarin anticoagulated atrial fibrillation patients: An ancillary analysis from the AMADEUS trial. *Int J Cardiol* 2016; 221: 379–382.

44. Mori N, Sotomi Y, Hirata A, et al. External Validation of the ORBIT Bleeding Score and the HAS-BLED Score in Nonvalvular Atrial Fibrillation Patients Using Direct Oral Anticoagulants (Asian Data from the DIRECT Registry). *Am J Cardiol* 2019; 124: 1044–1048.

45. Chao T-F, Lip GYH, Lin Y-J, et al. Incident Risk Factors and Major Bleeding in Patients with Atrial Fibrillation Treated with Oral Anticoagulants: A Comparison of Baseline, Follow-up and Delta HAS-BLED Scores with an Approach Focused on Modifiable Bleeding Risk Factors. *Thromb Haemost* 2018; 118: 768–777.

46. Fabritz L, Crijns HJGM, Guasch E, et al. Dynamic risk assessment to improve quality of care in patients with atrial fibrillation: The 7th AFNET/EHRA Consensus Conference. *Europace* 2021; 23: 329–344.

47. Hilkens NA, Algra A, Greving JP. Predicting major bleeding in ischemic stroke patients with atrial fibrillation. *Stroke* 2017; 48: 3142–3144.

48. Lip GYH, Skjøth F, Nielsen PB, et al. The HAS-BLED, ATRIA, and ORBIT Bleeding Scores in Atrial Fibrillation Patients Using Non-Vitamin K Antagonist Oral Anticoagulants. *Am J Med* 2018; 131: 574.e13-574.e27.

49. Gómez-Outes A, Lagunar-Ruíz J, Terleira-Fernández AI, et al. Causes of

Death in Anticoagulated Patients With Atrial Fibrillation. *J Am Coll Cardiol* 2016; 68: 2508–2521.

50. Steinberg BA, Simon DN, Thomas L, et al. Management of Major Bleeding in Patients With Atrial Fibrillation Treated With Non-Vitamin K Antagonist Oral Anticoagulants Compared With Warfarin in Clinical Practice (from Phase II of the Outcomes Registry for Better Informed Treatment of Atrial Fibrill. *Am J Cardiol* 2017; 119: 1590–1595.

FIGURES LEGENDS

Figure 1: Kaplan-Meier Curves for Bleeding Risk Scores

Legend: HAS-BLED) Log-Rank= 9.044, p=0.003; ORBIT) Log-Rank= 22.932, p<0.001.

Figure 2: Calibration Curves for Bleeding Risk Scores in EORP-AF Cohort

Legend: EORP-AF= EURObservational Research Programme in Atrial Fibrillation.

Figure 3: Illustrative Case for Baseline Bleeding Risk Evaluation in AF Patients

Legend: AF= Atrial Fibrillation; BP= Blood Pressure; ESC= European Society of Cardiology; NSAIDs= Non-Steroidal Anti-Inflammatory Drugs; OAC= Oral Anticoagulant.

Table 1: Baseline Characteristics of Patients Included in the Analysis

	EORP-AF LT General Registry N= 3018
Age, *years* median [IQR]	70 [62-77]
Female Sex, n (%)	1196 (39.6)
BMI, *kg/m²* median [IQR]	27.8 [25.0-31.5]
CrCl, *mL/min* median [IQR]	77.6 [58.3-100.0]
SBP, *mmHg* median [IQR]	130 [120-142]
DBP, *mmHg* median [IQR]	80 [70-88]
Chronic AF, n (%)	684 (22.7)
Heart Failure, n (%)	938 (31.1)
Hypertension, n (%)	1809 (59.9)
Diabetes Mellitus, n (%)	632 (20.9)
CAD, n (%)	642 (21.3)
PAD, n (%)	202 (607)
Stroke/TIA, n (%)	277 (9.2)
Previous Bleeding, n (%)	159 (5.3)
Liver Disease, n (%)	49 (1.6)
CKD, n (%)	209 (10.2)
CHA_2DS_2-VASc, median [IQR]	3 [2-4]

Legend: AF= Atrial Fibrillation; BMI= Body Mass Index; CAD= Coronary Artery Disease; CKD= Chronic Kidney Disease; CrCl= Creatinine Clearance; DBP= Diastolic Blood Pressure; EORP-AF= EURObservational Research Programme in Atrial Fibrillation;n iii909k988iiì,' IQR= Interquartile Range; LT= Long-Term; PAD= Peripheral Artery Disease; SBP= Systolic Blood Pressure; TIA= Transient Ischemic Attack.

Table 2: Bleeding Scores Distribution and Incidence of Major Bleeding

	HAS-BLED		ORBIT	
Mean (SD)	1.3 (1.0)		1.0 (1.2)	
Median [IQR]	1 [1-2]		1 [0-2]	
High Bleeding Risk, N (%)	356 (11.8%)		123 (4.1%)	
	N (%)	**MB (N, [IR])**	**N (%)**	**MB (N, [IR])**
0	605 (20.0)	2 (0.2)	1495 (49.5)	23 (0.8)
1	1199 (39.7)	20 (0.9)	732 (24.3)	10 (0.7)
2	858 (28.4)	24 (1.5)	357 (11.8)	10 (1.5)
3	290 (9.6)	9 (1.7)	311 (10.3)	8 (1.5)
4	59 (2.0)	4 (4.2)	80 (2.7)	4 (3.0)
5	7 (0.2)	1 (11.6)	38 (1.3)	5 (9.5)
6	-	-	5 (0.2)	0 (0)
7	-	-	-	-
8	-	-	-	-
9	-	-	-	-

Legend: IQR= Interquartile Range; IR= Incidence Rate; MB= Major Bleeding.

Table 3: Association between Bleeding Risk Scores and Risk of Major Bleeding Occurrence

	Univariate Analysis			Multivariate Analysis*		
	HR	**95% CI**	**p**	**HR**	**95% CI**	**p**
HAS-BLED						
Continuous Score	1.78	1.41-2.25	<0.001	1.74	1.37-2.21	<0.001
≥3 *(vs. <3)*	2.43	1.34-4.42	0.004	2.26	1.23-4.15	0.008
ORBIT						
Continuous Score	1.43	1.21-1.69	<0.001	1.42	1.20-1.68	<0.001
≥4 *(vs. <4)*	4.79	2.36-9.73	<0.001	4.62	2.25-9.46	<0.001

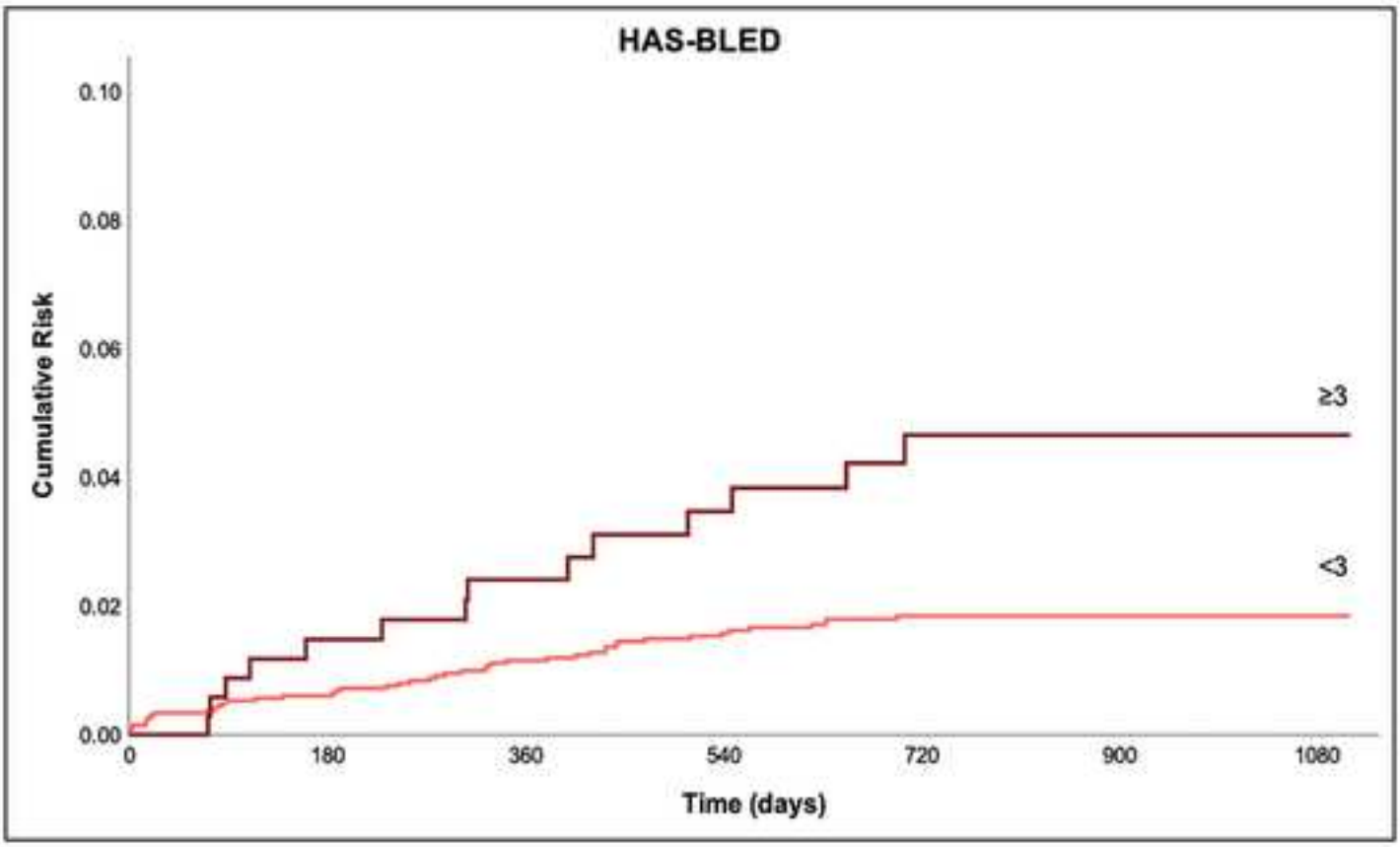
Legend: *adjusted for female sex, EHRA score and type of AF; AF= Atrial Fibrillation; CI= Confidence Interval; EHRA= European Heart Rhythm Association; HR= Hazard Ratio.

Table 4: Reclassification Analysis for Bleeding Risk Scores about Major Bleeding Occurrence

ORBIT vs. HAS-BLED	**IDI (95% CI)**	**p**	**NRI (95% CI)**	**p**	**MI (95% CI)**	**p**
1 year FU	-0.001	0.757	-0.069	0.465	-0.002	0.120
	(-0.009 / 0.009)		(-0.193 / 0.138)		(-0.004 / 0.002)	
2 years FU	-0.002	0.691	-0.117	0.093	-0.002	0.093
	(-0.018 / 0.015)		(-0.301 / 0.018)		(-0.013 / 0.001)	

Legend: CI= Confidence Interval; FU= Follow-Up; IDI= Integrated Discrimination Improvement; MI= Median Improvement; NRI= Net Reclassification Index.

Figure 1


HAS-BLED
Cumulative Risk
0.10
0.08
0.06
0.04
0.02
0.00
0
180
360
540
720
900
1080
Time (days)
≥3
<3

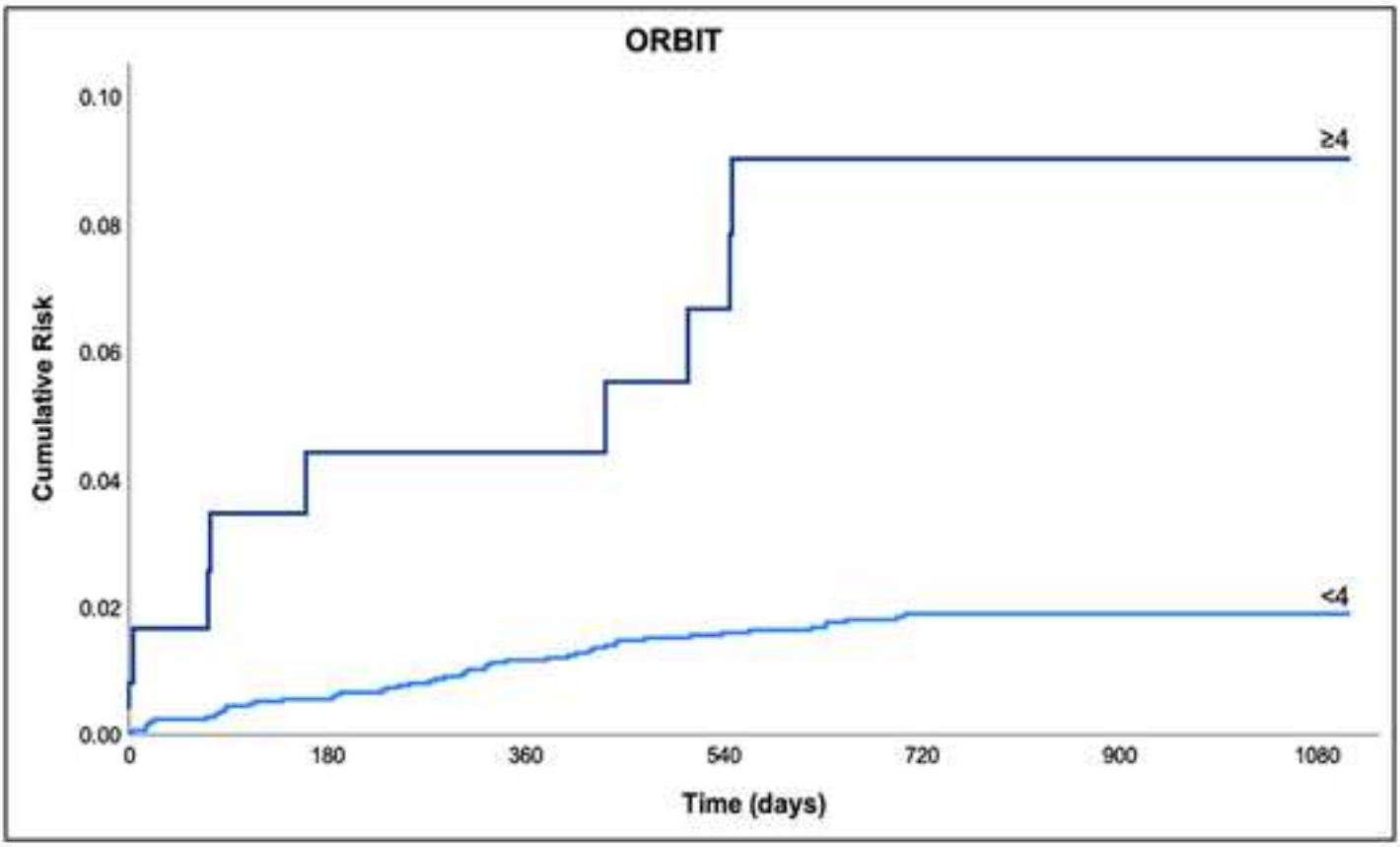

ORBIT
Cumulative Risk
0.10
0.08
0.06
0.04
0.02
0.00
0
180
360
540
720
900
1080
Time (days)
≥4
<4

Figure 2

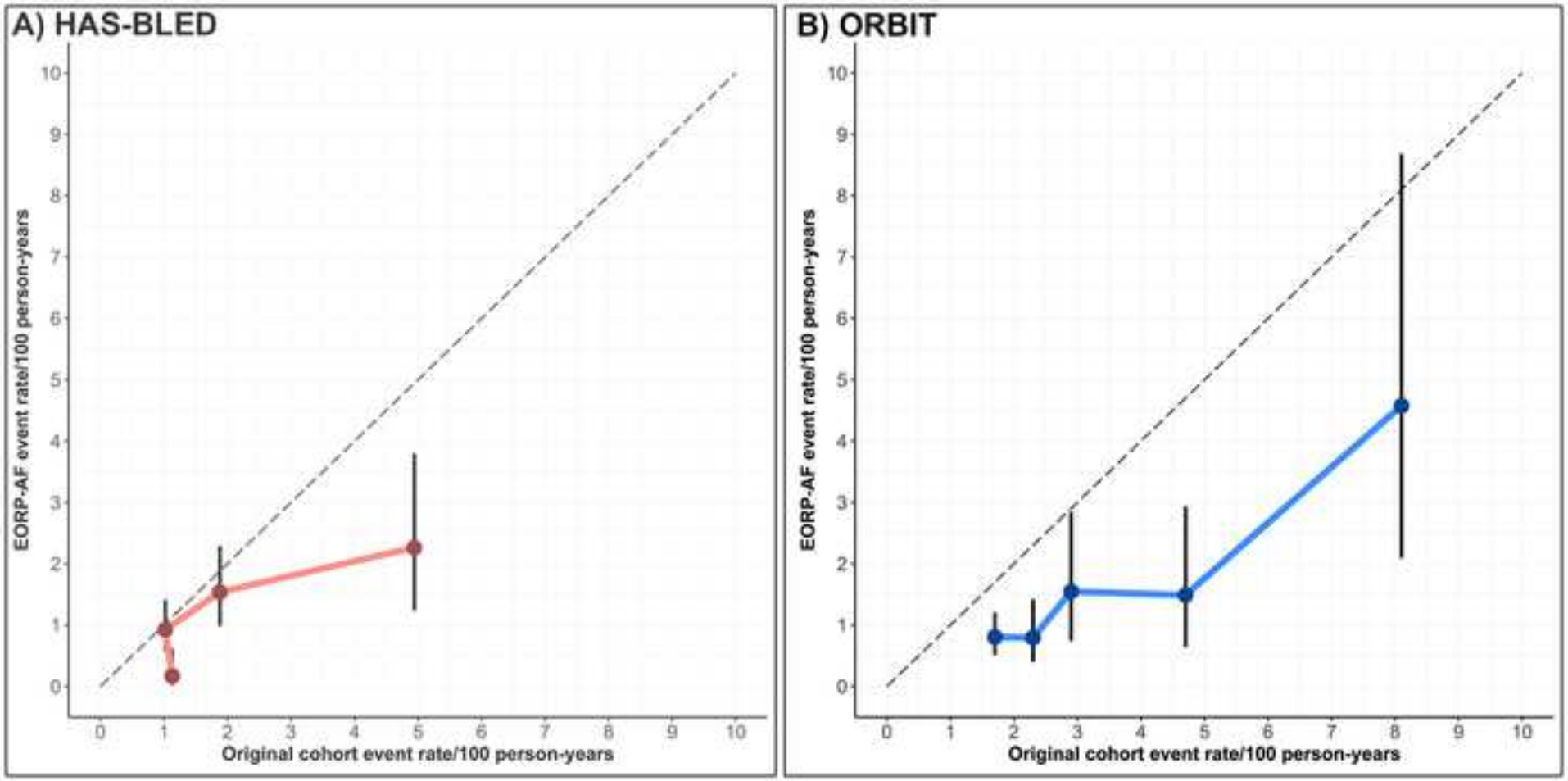
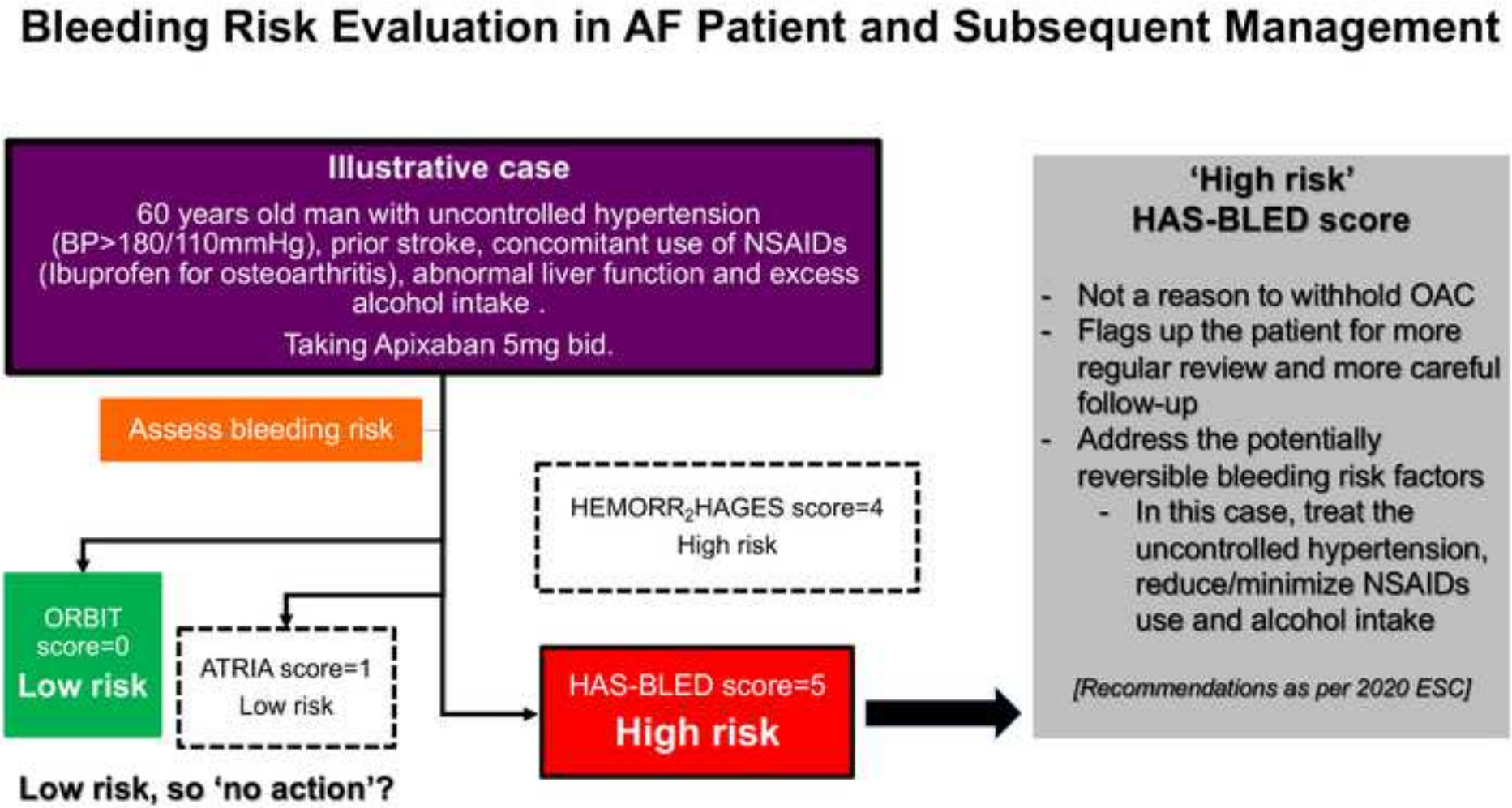

A) HAS-BLED
B) ORBIT
EORP-AF event rate/100 person-years
Original cohort event rate/100 person-years
0
1
2
3
4
5
6
7
8
9
10

Figure 3


Bleeding Risk Evaluation in AF Patient and Subsequent Management
Illustrative case
60 years old man with uncontrolled hypertension (BP>180/110mmHg), prior stroke, concomitant use of NSAIDs (Ibuprofen for osteoarthritis), abnormal liver function and excess alcohol intake .
Taking Apixaban 5mg bid.
Assess bleeding risk
ORBIT score=0
Low risk
ATRIA score=1
Low risk
HEMORR2HAGES score=4
High risk
HAS-BLED score=5
High risk
Low risk, so 'no action'?
'High risk'
HAS-BLED score
- Not a reason to withhold OAC
- Flags up the patient for more regular review and more careful follow-up
- Address the potentially reversible bleeding risk factors
  - In this case, treat the uncontrolled hypertension, reduce/minimize NSAIDs use and alcohol intake
[Recommendations as per 2020 ESC]

Comparison of HAS-BLED and ORBIT Bleeding Risk Scores in AF Patients treated with NOACs: A Report from the ESC-EHRA EORP-AF General Long-Term Registry

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Supplementary Materials

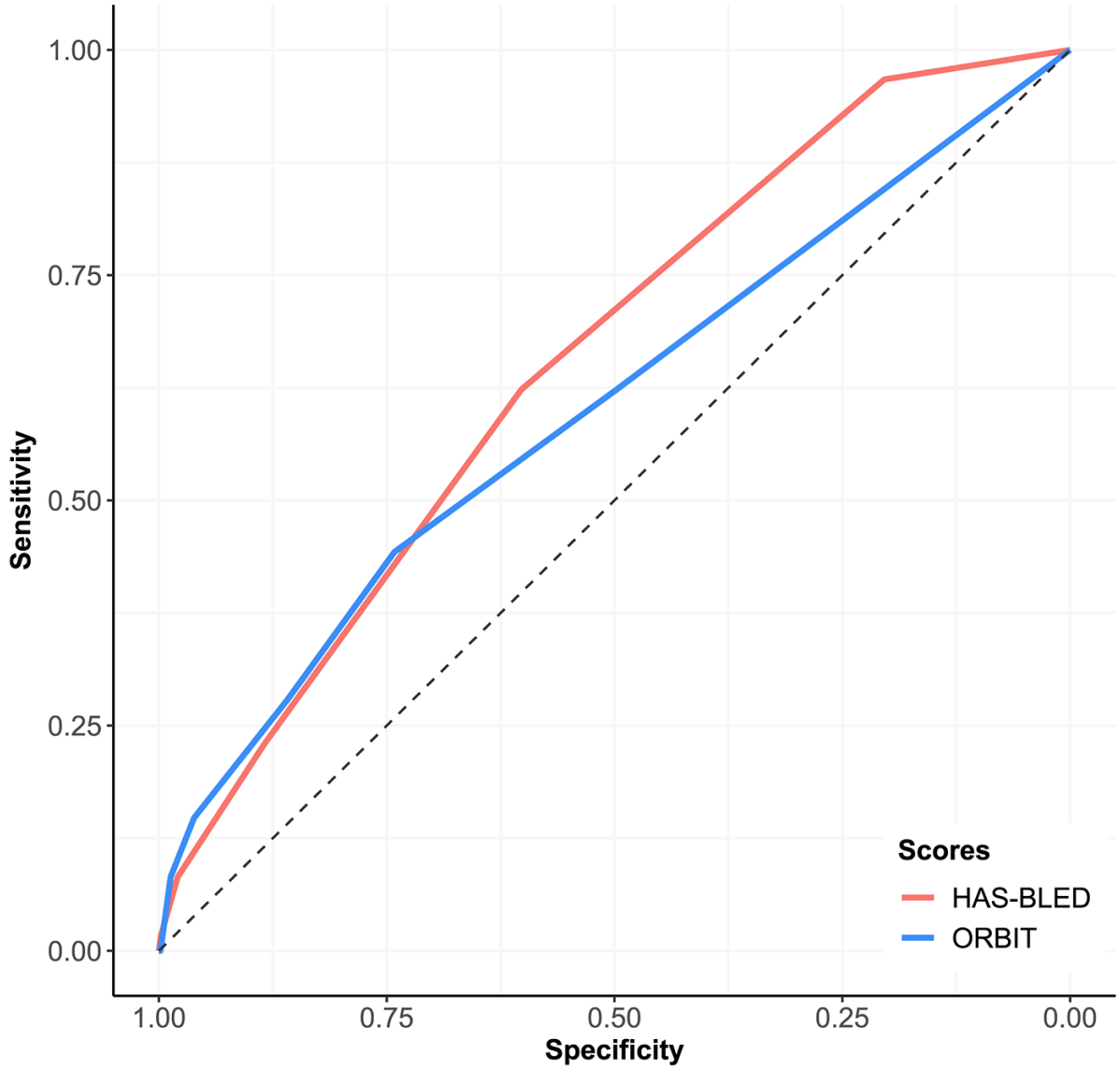
SUPPLEMENTARY METHODS

Assessment of Bleeding Risk Scores

The HAS-BLED score was developed in 2010 to devise a simple and clinically-driven risk score to assess major bleeding risk in AF patients treated with VKA[8]. One point each was allocated for the presence of hypertension, impaired renal or liver function, history of stroke, history of bleeding, labile international normalized ration (INR), elderly (age>65 years), concomitant use of antiplatelet agents or non-steroidal anti-inflammatory drugs and alcohol consumption (more than 8 units a week).

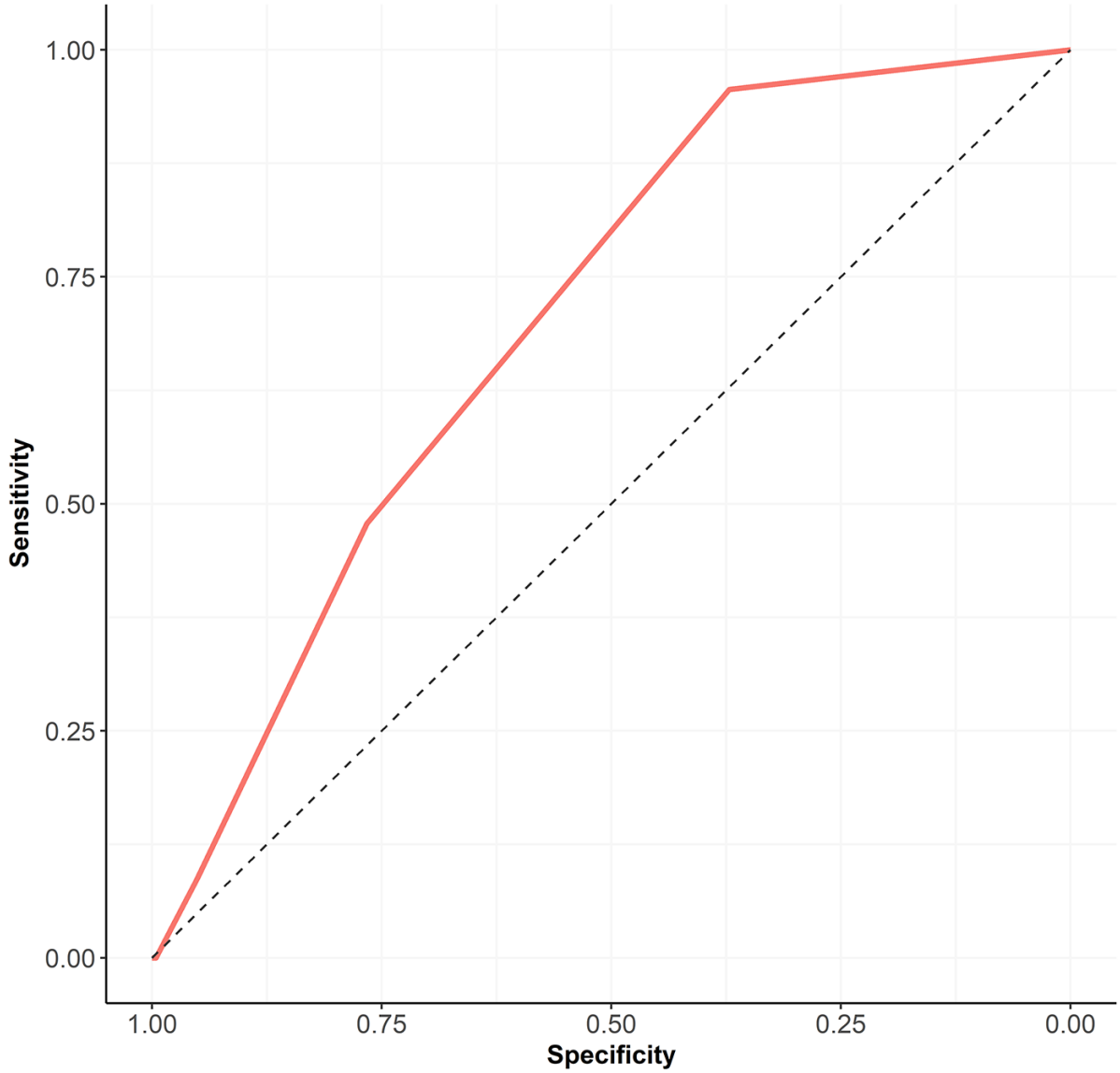
The ORBIT score was developed from the "Outcomes registry for better informed treatment of atrial fibrillation" study cohort[10,11], and calculated as follows: 1 point each for Age older than 74, insufficient kidney function (defined as estimated glomerular filtration rate below 60 mg/dL/1.73 m^2) and treatment with any antiplatelet drug, while 2 points were assigned to a positive clinical history for bleeding and the presence of anaemia or abnormal haemoglobin (<13 mg/dL for males and <12 mg/dL for females) or reduced haematocrit (<40% for males and <36% for females).

Figure S1: Bleeding Risk Scores ROC Curves for Major Bleeding Occurrence



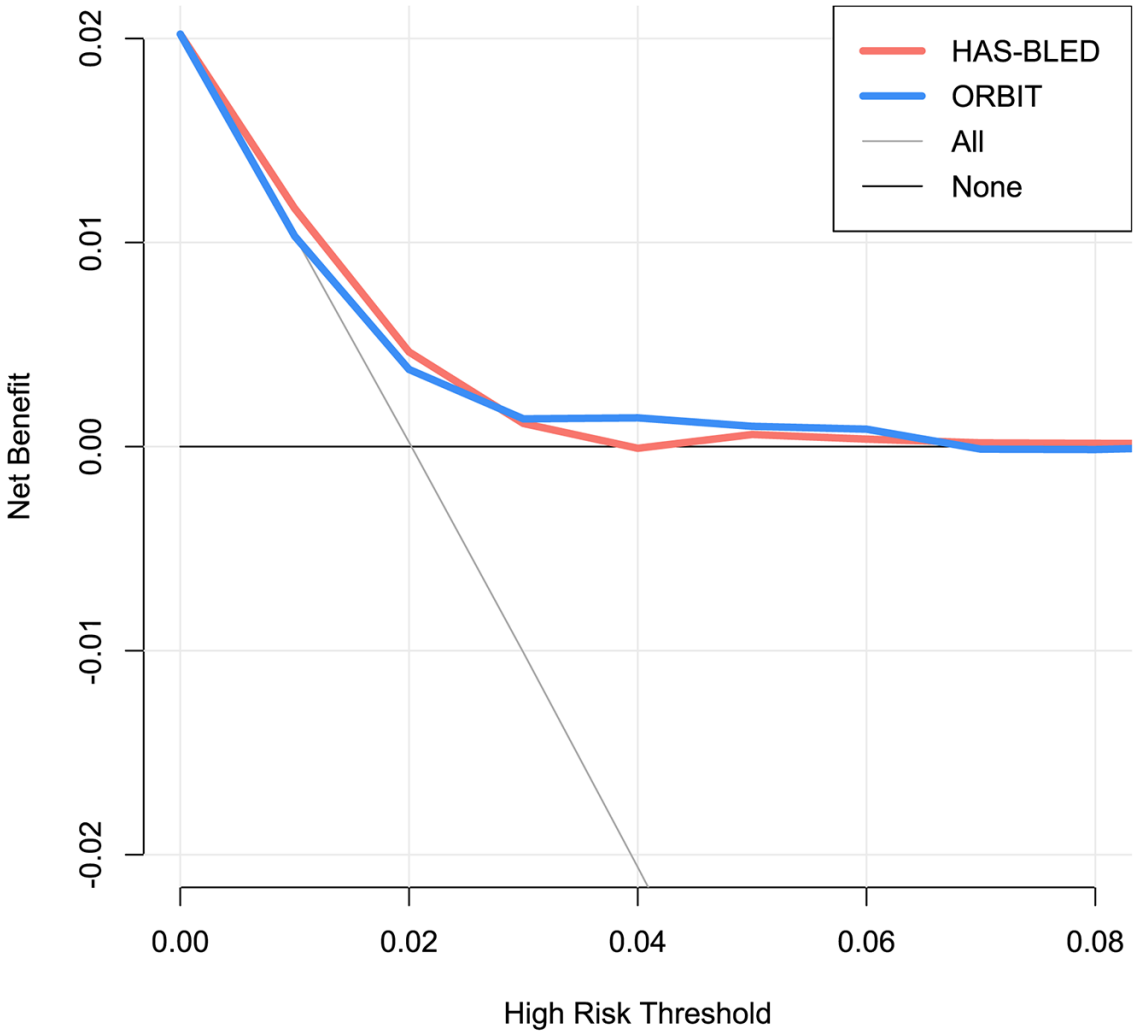
Legend: ROC= Receiving Operating Characteristics.

Figure S2: HAS-BLED Score ROC Curve in ORBIT Very Low Risk Patients



Legend: ROC= Receiving Operating Characteristics.

Figure S3: DCA Curves for Bleeding Risk Scores



Legend: DCA= Decision Curve Analysis.

APPENDIX

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