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Comparison of Bleeding Risk Scores in Patients with Atrial Fibrillation: Insights from the RE-LY Trial

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ABSTRACT

Background: Oral anticoagulation is the mainstay of stroke prevention in atrial fibrillation (AF), but must be balanced against the associated bleeding risk. Several risk scores have been proposed for prediction of bleeding events in patients with AF.

Objectives: To compare the performance of contemporary clinical bleeding risk scores in 18,113 patients with AF randomized to dabigatran 110 mg, 150 mg or warfarin in the RE-LY trial.

Methods: HAS-BLED, ORBIT, ATRIA and HEMORR$_2$HAGES bleeding risk scores were calculated based on clinical information at baseline. All major bleeding events were centrally adjudicated.

Results: There were 1,182 (6.5%) major bleeding events during a median follow-up of 2.0 years. For all the four schemes, high-risk subgroups had higher risk of major bleeding (all $p<0.001$). The ORBIT score showed the best discrimination with c-indices of 0.66, 0.66 and 0.62, respectively, for major, life-threatening and intracranial bleeding, which were significantly better than for the HAS-BLED score (difference in c-indices: 0.050, 0.053 and 0.048, respectively, all $p<0.05$). The ORBIT score also showed the best calibration compared with previous data. Significant treatment interactions between the bleeding scores and the risk of major bleeding with dabigatran 150 mg BD versus warfarin were found for the ORBIT ($p=0.0019$), ATRIA ($p<0.001$), and HEMORR$_2$HAGES ($p<0.001$) scores. HAS-BLED score showed a non-significant trend for interaction ($p=0.0607$).

Conclusions: Among the current clinical bleeding risk scores, the ORBIT score demonstrated the best discrimination and calibration. All the scores demonstrated, to a variable extent, an interaction with bleeding risk associated with dabigatran or warfarin.

Keywords: atrial fibrillation; anticoagulation treatment; major bleeding; bleeding risk scores; dabigatran.

INTRODUCTION

Atrial fibrillation (AF) is associated with a significant increase in risk for stroke and thromboembolic events which is variable between different patients [1–3]. Treatment with oral anticoagulant (OAC) is the cornerstone in prevention of thromboembolic events in AF patients at an increased risk of stroke [1]. However, OAC treatment is unavoidably associated with an increased risk of bleeding, regardless of OAC type used[4,5].

Non-vitamin K antagonist oral anticoagulants (NOACs) have been shown to be safer than warfarin in relation to major bleeding events, particularly intracranial hemorrhage[6]. All of the NOACs are now recommended in all guidelines[1–3,7,8] for stroke prevention in AF and in some guidelines in preference to vitamin K antagonist for the majority of AF patients[1,3,8].

Baseline evaluation of bleeding risk is mandatory [1–3,7,8] during the decision-making process of prescribing OAC therapy, as well as throughout follow-up, as bleeding risk may change over time. In recent years several clinical prediction scores have been developed and validated in large cohorts, and can be used as tools for bleeding risk evaluation in AF patients, namely, “Hypertension, Abnormal liver/renal function, Stroke, Bleeding, Labile International Normalized Ratio, Elderly, Drugs or alcohol” (HAS-BLED) [9], “Older age, Reduced haemoglobin/haematocrit/anaemia, Bleeding history, Insufficient kidney function, Treatment with platelets” (ORBIT) [10], “Anticoagulation and Risk Factors in Atrial Fibrillation” (ATRIA) Bleeding [11], “Hepatic or renal disease, Ethanol abuse, Malignancy history, Older (age >75), Reduced platelet count or function, Rebleeding risk, Hypertension, Anaemia, Genetic factors, Excessive fall risk, Stroke history” (HEMORR$_2$HAGES) [12] and

"Age, Biomarkers, Clinical history" (ABC)-bleeding[13] scores. Currently, most of the international guidelines propose the use of clinical tools to assess bleeding risk [1,3,7]. So far there are few studies which have focused on comparisons and validation of the different bleeding scores in patients treated with NOACs [10,14,15].

The aims of the current analyses are two-fold: (1) to compare the predictive performance of HAS-BLED, ORBIT, ATRIA and HEMORR$_2$HAGES bleeding scores in patients with AF enrolled in the "Randomized Evaluation of Long-term anticoagulant therapY" (RE-LY) Trial; and (2) to evaluate the interaction between predicted high risk of bleeding, according to the bleeding risk scores, and the effects on major bleeding by treatment with dabigatran (either 110 mg and 150 mg BID) or warfarin.

METHODS

Details about the study design and main results have been reported elsewhere[16,17]. Briefly, the RE-LY trial enrolled 18,113 patients with non-valvular AF who were randomized to receive OAC therapy with dabigatran 110 mg BID, dabigatran 150 mg BID or dose-adjusted warfarin (international normalized ratio (INR) target 2.0 to 3.0). The median duration of follow-up was 2.0 years. The study was conducted according to Good Clinical Practice recommendations and the Declaration of Helsinki. All enrolled patients were considered for this post-hoc analysis of the RE-LY trial.

The HAS-BLED, ORBIT, ATRIA and HEMORR$_2$HAGES scores were computed according to original definitions[9–12]. Details about the components, definitions, and risk categories

for the evaluated bleeding risk prediction scores are available in the web-only Supplementary Material.

The primary outcome for this analysis was the occurrence of major bleeding, the primary safety endpoint in the RE-LY trial, defined according to the original study protocol as a reduction in the hemoglobin level of at least 20 g per liter, transfusion of at least 2 units of blood or symptomatic bleeding in a critical area or organ[17]. Life-threatening bleeding and intracranial bleeding were considered as secondary outcomes. Life-threatening bleeding was a subcategory of major bleeding that consisted of fatal bleeding, symptomatic intracranial bleeding, bleeding with a decrease in the hemoglobin level of at least 50 g per liter, or bleeding requiring transfusion of at least 4 units of blood or inotropic agents or necessitating surgery[17]. All bleeding events were centrally adjudicated by an independent clinical events committee blinded to treatment assignment. The current analyses have been performed incorporating the additional events reported and adjudicated after the release of the study main results[18].

Statistical Analysis

Categorical variables have been reported as counts and percentages, while continuous variables have been reported as median and interquartile range. Comparisons between categorical variables have been performed with chi-squared test, whilst comparisons between continuous variables were performed according to the Wilcoxon rank sum test. Outcomes are expressed as annualized incidence rates.

The discriminative ability of the scores was assessed and compared using Harrell's C-index. Confidence interval for differences between C-indexes was obtained using 1000 bootstrap

samples. Calibration was evaluated by plots of major bleeding events rates per 100 patient-years (95% confidence interval) observed in the RE-LY trial vs. the previously published event rates from the original derivation cohorts. Interactions between study treatments and risk scores (in clinically meaningful risk categories as well as in continuous form) regarding study outcomes were evaluated by Cox proportional hazards models. As reported in the Supplementary Materials, a sensitivity analysis for HAS-BLED with alternative definition of "Labile INR" criterion was performed. A 2-sided $p<0.05$ was considered statistically significant and since all analyses were exploratory, there were no adjustments for multiple comparisons. All analyses were performed with SAS software, version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

A total of 1182 (6.5%) major bleeding events occurred and were adjudicated, with an overall annual rate of 3.31%/year. Among these events, 47.0% (n= 555) were life-threatening bleeding events with an overall annual rate of 1.55%/year. Intracranial bleeds occurred in 157 (13.3% of major bleeding events), with an overall annual rate of 0.44%/year events. Clinical characteristics of patients according to major bleeding occurrence are summarized in Table 1.

As previously reported elsewhere, patients reporting a major bleeding occurrence were more likely to be older, hypertensive and with a previous history of stroke/transient ischemic attack/systemic embolic event[17,19]. Patients who experienced major bleeding had a higher thromboembolic risk ($p<0.0001$) (Table 1). Results were similar when separately analyzed by randomized treatment (Table S1).

Risk Score Distribution and Bleeding Outcomes

HAS-BLED, ORBIT, ATRIA and HEMORR$_2$HAGES median scores were higher (all $p<0.0001$) in patients that experienced major bleeding compared to those patients who did not (Table 2). Accordingly, the proportion of patients assigned to the high-risk category was consistently higher for those that reported major bleeding during follow-up for all four bleeding risk scores (all $p<0.0001$).

Analysing the bleeding risk scores distribution in relation to the randomized treatment yielded similar results with higher values for the bleeding risk scores in patients that experienced major bleeding (Table S2). Similarly, the proportion allotted to high risk

categories within each score was higher among the patients that reported a major bleeding occurrence for all the randomized treatments (Table S2).

Discriminative Performance

Predictive performances of the bleeding risk scores are reported in Table 3. All bleeding risk scores showed a significant, albeit, modest predictive capacity. Among the overall cohort, the best discrimination in predicting major bleeding occurrence was shown using the ORBIT score (c-index: 0.66). Stratifying the results according to the randomized treatment, all the bleeding risk scores demonstrated significant predictive ability for all randomized treatment groups (Table 3). The ORBIT score also demonstrated the best discriminative ability across randomized OAC treatment groups (c-indexes: 0.68, 0.70 and 0.62, for dabigatran 110 mg, dabigatran 150 mg and warfarin, respectively). Similar results were obtained for life-threatening bleeding occurrence. For the intracranial bleeding outcome, all the scores had lower predictive ability, both in the overall population and in the randomized treatments subgroups (Table 3). The ORBIT score was consistently the best predictor for intracranial bleeding among the three treatment subgroups, while the predictive ability of the HAS-BLED, ATRIA and HEMORR$_2$HAGES was found to be broadly non-significant among patients randomized to both dabigatran 110 mg and dabigatran 150 mg.

When comparing the discriminative abilities of the four bleeding scores (Table 4), the ORBIT score was consistently found to be significantly better than HAS-BLED, across the three bleeding outcomes (differences in c-indices: 0.050, 0.053 and 0.048, for major bleeding, life-threatening bleeding and intracranial bleeding, respectively). The ATRIA score performed better than HAS-BLED only for prediction of major bleeding, while differences in

the c-indexes for the other outcomes were non-significant. HEMORR$_2$HAGES performed similarly to HAS-BLED for all the outcomes considered (Table 4).

Calibration Analysis

Evaluation of calibration, the comparison between estimated and actually observed event rates, for the four bleeding scores demonstrated that the ORBIT score had the best agreement over the range of bleeding risk when compared to the original derivation cohort [Figure 1]. Conversely, the ATRIA score showed the largest mismatch in calibration. The ATRIA and HAS-BLED scores, to different degrees, tended to overestimate the risk of bleeding. The HEMORR$_2$HAGES score underestimated the risk of bleeding events, in particularly for those patients with a higher predicted risk [Figure 1].

Treatment Effect Interactions with Bleeding Risk Scores

Major bleeding incidence rates progressively increased according to increasing scores for all the four bleeding risk score schemes [Figure 2, Panel A]. Compared to warfarin, incidence rates were found to be higher for patients assigned to dabigatran 150 mg BID according to the increasing score for all the schemes (p for interaction =0.0122, $p<0.0001$, $p<0.0001$ and $p<0.0001$ respectively for HAS-BLED, ORBIT, ATRIA and HEMORR$_2$HAGES). Similar results were reported for life-threatening bleeding [Figure 2, Panel B].

In patients assigned to dabigatran 110 mg BID, higher incidence rates were evident compared to warfarin based on increasing ORBIT and ATRIA scores (p for interaction=0.0051 and p=0.0047, respectively) [Figure 2, Panel A]. No significant interactions were found for life-threatening bleeding for dabigatran 110 mg compared to warfarin [Figure 2, Panel B] or intracranial bleeding for both dabigatran 110 mg and 150 mg [Figure 2, Panel C].

The interaction analyses demonstrated that the ORBIT, ATRIA and HEMORR$_2$HAGES scores had a significant interaction with treatment on major bleeding when comparing patients assigned to dabigatran 150 mg with those randomized to receive warfarin (p=0.0019, p<0.0001 and p<0.0001, respectively) [Figure 3, Upper Panel]. Conversely, the HAS-BLED score showed a non-significant trend for interaction (p=0.0607) [Figure 3, Upper Panel]. Only the ATRIA score showed a significant treatment interaction in patients randomized to dabigatran 110 mg compared to those assigned to warfarin (p=0.0097) [Figure 3, Lower Panel].

Similarly, ORBIT, ATRIA and HEMORR$_2$HAGES high risk categories were found to be associated with life-threatening bleeding occurrence in patients assigned to dabigatran 150 mg (p=0.0266, p=0.0021 and p=0.0073). HAS-BLED showed a trend in association, despite not reaching statistical significance (p=0.0574) (Table S3). No significant treatment interaction for life-threatening bleeding was found when comparing dabigatran 110 mg and warfarin according the four bleeding scores. No significant interaction was detected for the three randomized treatments groups across the four scores for the intracranial bleeding occurrence (Table S3).

Sensitivity Analysis

A sensitivity analysis was conducted for HAS-BLED using an alternative definition for labile INR (Tables S4-S5), according the INR value at randomization (see Supplementary Methods in Supplementary Materials). In this sensitivity analysis, a significant treatment interaction for the HAS-BLED score and major bleeding occurrence was found, with HAS-BLED high-risk category patients assigned to receive dabigatran 150 mg, with a significant higher risk of

major bleeding occurrence compared to warfarin patients (p=0.0050) (Table S4, Right Column).

DISCUSSION

In this post-hoc analysis of the RE-LY cohort, we found that the HAS-BLED, ORBIT, ATRIA and HEMORR$_2$HAGES bleeding scores had a significant, albeit modest, discriminative capacity in predicting major and life-threatening bleeding occurrences. All the bleeding risk scores identified groups with different risks of major and life-threatening bleeding outcomes, independently of treatment with dabigatran or warfarin. Among them, the ORBIT score demonstrated the best discriminative ability and the best calibration. The ORBIT, ATRIA and HEMORR$_2$HAGES scores showed significant treatment interactions, comparing dabigatran 150 mg BID and warfarin according to the predicted bleeding risk at baseline, for the occurrence of major and life-threatening bleeding events. The HAS-BLED score showed a significant treatment interaction only when computed using the alternative "Labile INR" criterion, related to the current INR at randomization.

Occurrence of major bleeding events is the most feared complication for physicians prescribing OAC[20] and physicians may often overestimate patients' bleeding risk, leading to OAC under-prescription[21] and under-dosing [22]. Data from a large observational trial in USA, the "Outcomes Registry for Better Informed Treatment of Atrial Fibrillation" study, showed that the high risk of bleeding, as well as the previous history of bleeding, were amongst the most prevalent reasons for not prescribing OAC[23]. Similarly, data from the same cohort showed that the high risk of bleeding was one of the main reasons leading to

OAC discontinuation[24]. Indeed, the concern about major bleeding seems to disproportionally outweigh the risk of stroke among some prescribing physicians[25]. Nonetheless, high risk of bleeding alone should not be a sufficient reason to withhold OAC treatment. All major current guidelines strongly emphasize that all patients should be evaluated for bleeding risk at baseline[1–3,7,8], and recommend that modifiable and potentially modifiable bleeding risk factors are addressed in order to minimize the risk of bleeding[1]. It is proposed that patients identified as at high bleeding risk are monitored more closely. Bleeding risk should therefore not be considered as definite, but rather as a continuum, and bleeding risk assessment should routinely be repeated at follow-up visits and managed appropriately. In this setting, it is therefore fundamental to use well-calibrated and validated bleeding risk scores. Another important issue concerning clinical risk scores is the ease of use which may influence the uptake and generalizability of a score. However, the growing use of digital calculators and electronic medical charts in current practice will likely increase and facilitate the implementation of more precise risk models and integrated decision support tools.

Bleeding risk prediction scores are considered by international guidelines as useful tools to identify those patients with a prevalent bleeding risk[1,3,7]. The performance of HAS-BLED, ATRIA and HEMORR$_2$HAGES scores have been evaluated and validated in several previous studies [10,26–30]. Several comparisons have been performed between the bleeding risk scores among AF patients treated with vitamin K antagonist, in several different scenarios, both from real-life cohorts [31,32] and post-hoc or prospective analyses of randomized controlled trials[14,33–35] and have demonstrated overall modest predictive capacity for all the scores [31–35], with several of the previous analyses indicating that the HAS-BLED score performs better in those patients treated with vitamin K antagonist [31,33–35].

To date there is limited data on the use of bleeding risk scores in patients treated with NOACs. The present analyses demonstrate that all the bleeding risk scores can separate groups with different risks of major bleeding and life-threatening bleeding in a large cohort of patients treated with either warfarin or a NOAC, namely dabigatran in the present study. The ORBIT score was validated in the "Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation" study and demonstrated slightly better discriminative capacity than the HAS-BLED and ATRIA bleeding scores (c-indices: 0.67, 0.64, 0.66, respectively)[10]. Furthermore, the ORBIT score was also shown to outperform the HAS-BLED score in another large cohort of patients treated with apixaban, in a subgroup analysis derived from the "Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation" study[13]. In the current RE-LY cohort, the ORBIT score showed the best predictive ability and calibration. Together with the previous evidence[10,13], our data seem to suggest that the ORBIT score has superior discrimination and calibration properties than HAS-BLED when applied to mixed cohorts of patients, treated with both warfarin and NOACs.

The ORBIT, ATRIA, HEMORR$_2$HAGES scores and to some extent the HAS-BLED score, managed to identify a group of high-risk patients that, when treated with dabigatran 150 mg were more likely to experience a major bleed. Conversely, the same high-risk patients had a lower bleeding risk when treated with dabigatran 110 mg. This clearly illustrates how dabigatran can be a safe alternative for AF patients even at a high risk of bleeding by using a more "personalized treatment" based on one of these bleeding scores when considering the most suitable dose.

Limitations

The main limitation of the current analysis is its retrospective nature and therefore the original study design was not specifically powered to detect differences in the subgroups under consideration. In addition, this analysis was performed on a cohort of AF patients from a randomized controlled trial, thus our results may not be completely generalizable to the overall AF population. Also, additional cardiovascular biomarkers were not available in all patients and therefore the recently developed ABC-bleeding risk score[13] was not included in the present analyses. Finally, despite reporting overall significant predictive properties, all the scores demonstrated a rather modest prediction ability.

CONCLUSIONS

All the bleeding risk scores identified patient groups with different risks of major bleeding and life-threatening bleeding with modest and variable discriminative ability. The ORBIT score demonstrated superior discrimination and calibration in this large randomized clinical trial of AF patients. All the bleeding risk scores demonstrated, to a variable extent, a significant interaction with the bleeding risk associated with dabigatran or warfarin.

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DISCLOSURES OF INTEREST

MP reports small consulting fee from Boehringer Ingelheim. ZH reports lecture fees from Boehringer Ingelheim and Bristol-Myers Squibb/Pfizer; consulting fees from Bristol-Myers Squibb/Pfizer, Roche Diagnostics, and Merck, Sharp and Dohme. SJC reports consulting fees, speaker fees and research grants from Boehringer Ingelheim, Bristol-Myers Squibb, Bayer, Portola; consulting fees and research grants from Sanofi-Aventis; research grants from Boston Scientific. JWE reports grants and honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer, Daiichi-Sankyo, GlaxoSmithKline, Janssen, Sanofi-Aventis; honoraria from Eli Lilly. MDE reports consulting fees from Boehringer Ingelheim, Pfizer, Sanofi, Bristol-Myers Squibb, Portola, Bayer, Daiichi-Sankyo, Medtronics, Aegerion, Merck, Johnson & Johnson, Gilead, Janssen Scientific Affairs, Pozen Inc., Amgen, Coherex, Armatheon. DAL reports investigator-initiated educational grants from Bristol Myers Squibb and Boehringer Ingelheim, and has been a speaker and consultant for Boehringer Ingelheim, Bayer, and Bristol Myers Squibb/Pfizer. JO reports consulting and lecture fees from Boehringer Ingelheim, Bayer, Bristol-Myers Squibb, Pfizer. SY reports consulting fees, lecture fees and grant support from Boehringer Ingelheim, AstraZeneca, Bristol-Myers Squibb, Sanofi- Aventis, Bayer, Cadila. LW reports institutional research grants, consultancy fees, lecture fees, and travel support from Bristol- Myers Squibb/Pfizer, AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim; institutional research grants from Merck & Co, Roche; consultancy fees from Abbott. Other authors have nothing to disclose.

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FIGURE LEGENDS

Figure 1: Bleeding Risk Scores Calibration Between Derivation Cohorts and RE-LY Cohort Event Rates

Figure 2: Major Bleeding Incidence Rates According Bleeding Risk Scores and Randomized Treatment

Legend: Panel A) Major Bleeding; Panel B) Life-Threatening Bleeding; Panel C) Intracranial Bleeding; DE110= dabigatran etexilate 110 mg; DE150= dabigatran etexilate 150 mg; W= warfarin.

Figure 3: Forest Plots for Treatment Interactions in Major Bleeding Occurrence According Bleeding Risk Scores Categories

Legend: DE110= dabigatran etexilate 110 mg; DE150= dabigatran etexilate 150 mg.

Table 1: Baseline Characteristics According Major Bleeding Occurrence

	Major Bleeding		**p-value**
	Yes	**No**	
	N=1182	N=16931	
Age, (*years*) median [IQR]	76 [71-80]	72.0 [66-77]	<0.0001
Age ≥75 years, n (%)	670 (56.7)	6568 (38.8)	<0.0001
Female, n (%)	413 (34.9)	6185 (36.5)	0.27
SBP, (*mmHg*) median [IQR] (*18086)**	130 [118-140]	130 [120-140]	0.0046
CrCL, (*mL/min*), median [IQR] (*17375)**	59.9 [46.9-75.7]	69.1 [53.9-87.4]	<0.0001
Hypertension, n (%)	970 (82.1)	13313 (78.6)	0.0053
Diabetes Mellitus, n (%)	354 (29.9)	3867 (22.8)	<0.0001
CAD, n (%)	449 (38.0)	4585 (27.1)	<0.0001
Previous Stroke/SEE/TIA, n (%)	289 (24.5)	3664 (21.6)	0.0238
Symptomatic HF (NYHA≥2), n (%)	325 (27.5)	4579 (27.1)	0.73
CrCL Category, n (%) (*17375)**			<0.0001
<50 mL/min	360 (31.4)	3060 (18.9)	
50-79 mL/min	554 (48.3)	7743 (47.7)	
≥80 mL/min	234 (20.4)	5424 (33.4)	
History of Fall, n (%)	205 (17.4)	1842 (10.9)	<0.0001
Anemia, n (%)	327 (27.7)	2146 (12.7)	<0.0001
Malignancy, n (%)	171 (14.5)	1714 (10.1)	<0.0001

Previous VKA Use, n (%)			0.32
Experienced	603 (51.0)	8381 (49.5)	
Naive	579 (49.0)	8547 (50.5)	
Concomitant ASA, n (%)	556 (47.0)	6597 (39.0)	<0.0001
Statins, n (%)	576 (48.7)	7481 (44.2)	0.0024
H2 Blockers, n (%)	65 (5.5)	693 (4.1)	0.0196
ACEi/ARB, n (%)	805 (68.1)	11178 (66.0)	0.14
Amiodarone, n (%)	113 (9.6)	1863 (11.0)	0.12
PPI, n (%)	225 (19.0)	2342 (13.8)	<0.0001
$CHADS_2$, median [IQR]	2 [2-3]	2 [1-3]	<0.0001

Legend: *total number of patients with available data about the covariate; ACEi= angiotensin converting enzyme inhibitor; ARBs= angiotensin receptor blocker; ASA= acetylsalicylic acid; CAD= coronary artery disease; CrCl= creatinine clearance; HF= heart failure; IQR= interquartile range; PPI= proton pump inhibitor; SBP= systolic blood pressure; SEE= systemic embolic event; TIA= transient ischemic attack; VKA= vitamin K antagonist.

Table 2: Bleeding Risk Score Categories According to Major Bleeding Occurrence

	Overall	**Major bleeding**		**p-value**
	N=18113	**No**	**Yes**	
		N=16931	N=1182	
HAS-BLED, median [IQR]	2 [1-2]	2 [1-2]	2 [1-3]	<0.0001
HAS-BLED Categories, n (%)				<0.0001
Low (0-2)	14684 (81.1)	13874 (81.8)	810 (69.7)	
High (>2)	3429 (18.9)	3077 (18.2)	352 (30.3)	
ORBIT, median [IQR]	1 [1-2]	1 [1-2]	2 [1-3]	<0.0001
ORBIT Categories, n (%)				<0.0001
Low (0-2)	14203 (78.4)	13517 (79.7)	686 (59.0)	
Intermediate (3)	2371 (13.1)	2144 (12.6)	227 (19.5)	
High (>3)	1539 (8.5)	1290 (7.6)	249 (21.4)	
ATRIA, median [IQR]	0 [0-2]	0 [0-2]	2 [0-3]	<0.0001
ATRIA Categories, n (%)				<0.0001
Low (0-4)	16746 (92.5)	15787 (93.1)	959 (82.5)	
Intermediate/High (≥4)	1367 (7.5)	1164 (6.9)	203 (17.5)	
HEMORR$_2$HAGES, median [IQR]	1 [0-2]	1 [0-2]	1 [1-2]	<0.0001
HEMORR$_2$HAGES Categories, n (%)				<0.0001
Low (0-1)	12874 (71.1)	12239 (72.2)	635 (54.6)	
Intermediate (2-3)	4932 (27.2)	4449 (26.2)	483 (41.6)	
High (>3)	307 (1.7)	263 (1.6)	44 (3.8)	

Legend: ATRIA= Anticoagulation and Risk Factors in Atrial Fibrillation; HAS-BLED= Hypertension, Abnormal liver/renal function, Stroke, Bleeding, Labile International Normalized Ratio, Elderly, Drugs or alcohol; HEMORR$_2$HAGES= Hepatic or renal disease, Ethanol abuse, Malignancy history, Older (age >75), Reduced platelet count or function, Rebleeding risk, Hypertension, Anaemia, Genetic factors, Excessive fall risk, Stroke history; IQR= interquartile range; ORBIT= Older age, Reduced haemoglobin/haematocrit/anaemia, Bleeding history, Insufficient kidney function, Treatment with platelets.

Table 3: Discriminative Abilities for the Bleeding Risk Scores According to Randomized Treatment and Outcomes Occurrences

		C-index (95% CI)			
Outcome	**Risk Score***	**Overall**	**Dabigatran 110**	**Dabigatran 150**	**Warfarin**
Major Bleeding	*HAS-BLED*	0.62 (0.60-0.63)	0.61 (0.58-0.64)	0.64 (0.62-0.67)	0.59 (0.57-0.62)
	ORBIT	0.66 (0.65-0.68)	0.68 (0.65-0.71)	0.70 (0.68-0.73)	0.62 (0.59-0.64)
	ATRIA	0.64 (0.62-0.65)	0.64 (0.61-0.67)	0.67 (0.65-0.70)	0.59 (0.57-0.62)
	HEMORR$_2$HAGES	0.62 (0.61-0.64)	0.61 (0.58-0.64)	0.66 (0.64-0.69)	0.59 (0.56-0.62)
Life-Threatening Bleeding	*HAS-BLED*	0.61 (0.59-0.64)	0.60 (0.56-0.64)	0.65 (0.61-0.69)	0.59 (0.55-0.63)
	ORBIT	0.66 (0.64-0.68)	0.67 (0.63-0.71)	0.71 (0.68-0.75)	0.62 (0.58-0.65)
	ATRIA	0.63 (0.61-0.66)	0.63 (0.58-0.67)	0.68 (0.64-0.72)	0.59 (0.56-0.63)
	HEMORR$_2$HAGES	0.62 (0.60-0.64)	0.61 (0.57-0.66)	0.66 (0.63-0.70)	0.59 (0.56-0.62)

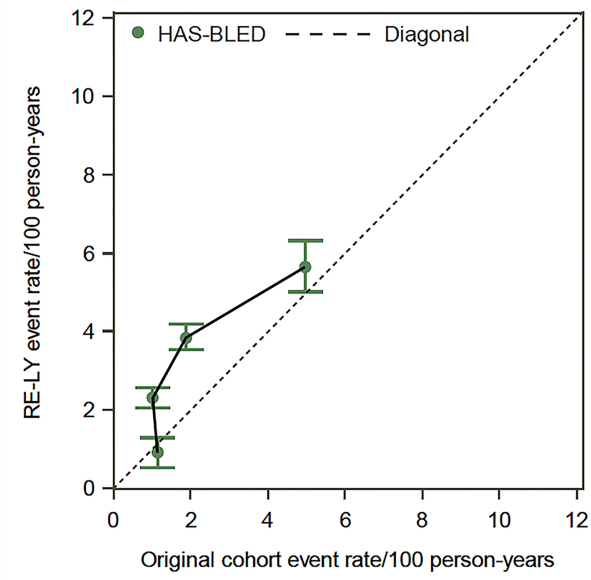
Intracranial Bleeding	*HAS-BLED*	0.56 (0.52-0.61)	0.52 (0.42-0.63)	0.56 (0.48-0.64)	0.57 (0.52-0.63)
	ORBIT	0.62 (0.57-0.66)	0.63 (0.55-0.72)	0.60 (0.50-0.69)	0.62 (0.57-0.67)
	ATRIA	0.58 (0.54-0.63)	0.59 (0.50-0.69)	0.59 (0.50-0.68)	0.58 (0.52-0.63)
	HEMORR$_2$HAGES	0.59 (0.55-0.64)	0.54 (0.44-0.65)	0.61 (0.52-0.70)	0.60 (0.55-0.66)

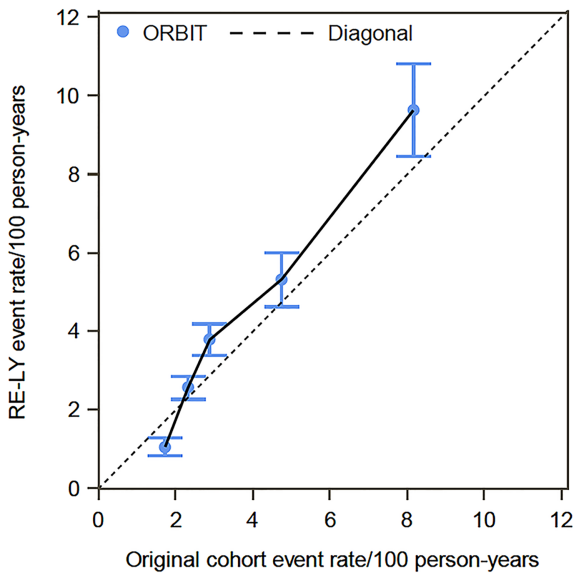
Legend: *See Table 2 for risk scores acronyms; CI= confidence interval.

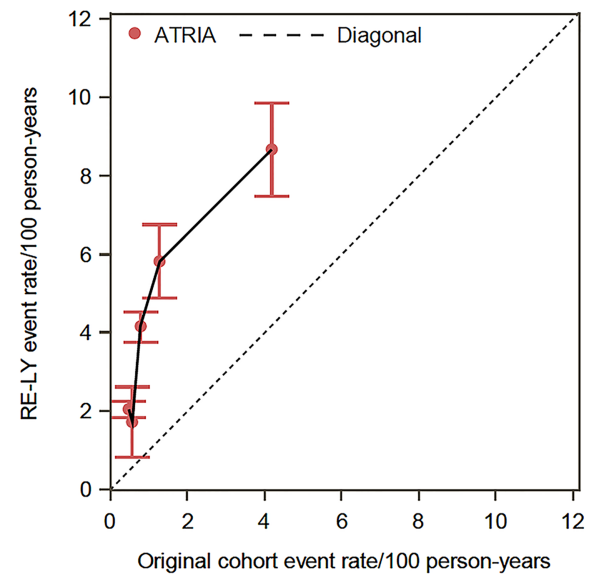
Table 4: Discriminative Difference Compared to HAS-BLED According Outcomes*

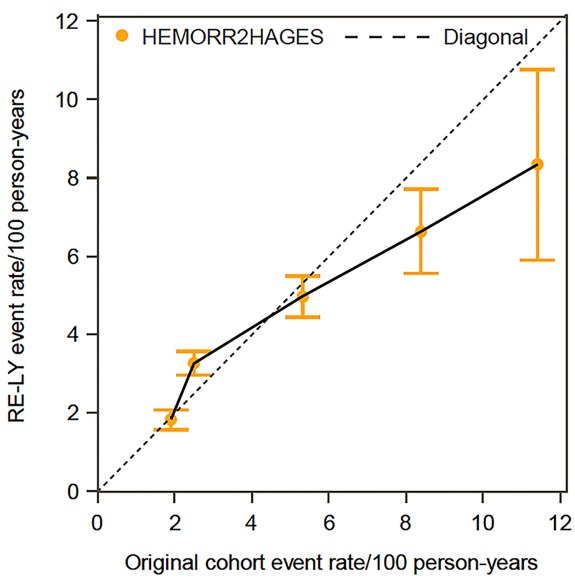
	Difference in C-index (95% CI) *vs.* HAS-BLED		
	Major Bleeding	**Life-Threatening Bleeding**	**Intracranial Bleeding**
ORBIT	**0.050 (0.036, 0.063)**	**0.053 (0.009, 0.092)**	**0.048 (0.026, 0.067)**
ATRIA	**0.021 (0.005, 0.036)**	0.020 (-0.032, 0.072)	0.018 (-0.008,0.042)
HEMORR$_2$HAGES	0.006 (-0.010, 0.020)	0.030 (-0.012, 0.076)	0.007 (-0.015, 0.029)

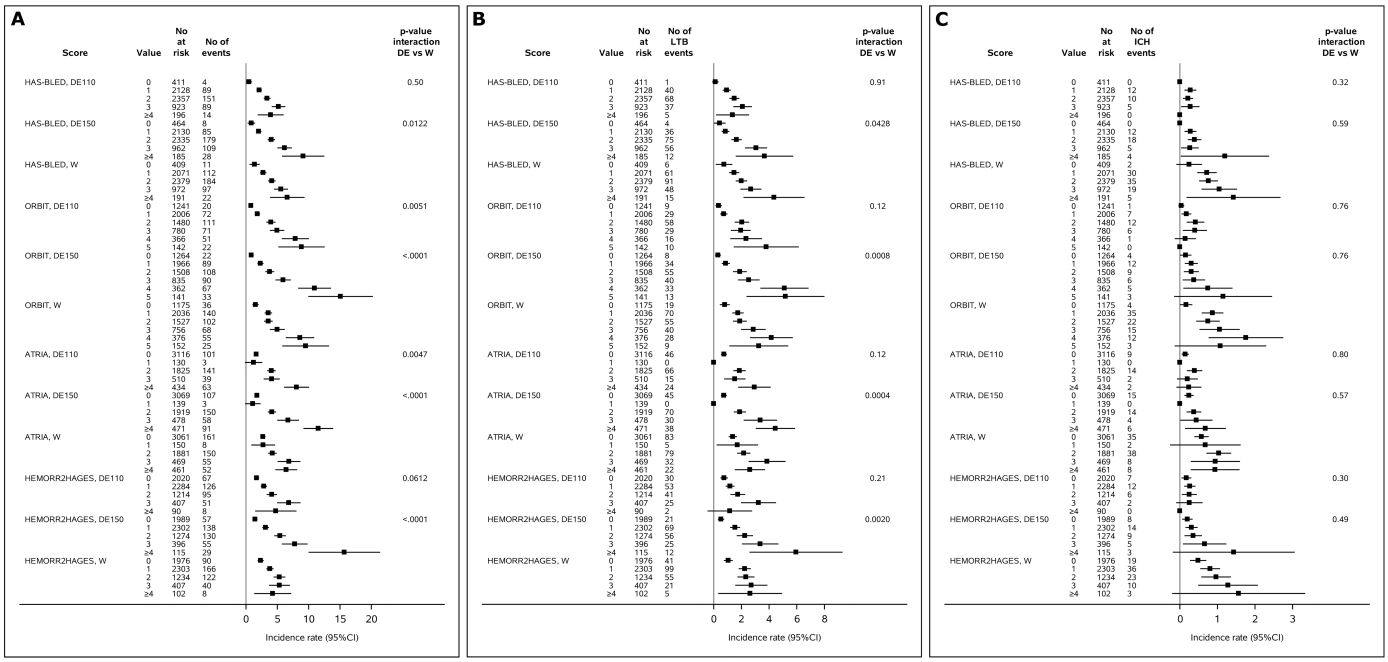
Legend: *See Table 2 for risk scores acronyms; †Bold indicates statistically significant results. CI= confidence interval.


HAS-BLED
Diagonal
RE-LY event rate/100 person-years
Original cohort event rate/100 person-years
0
2
4
6
8
10
12

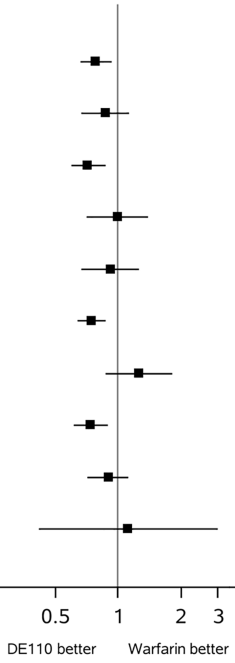

ORBIT
Diagonal
RE-LY event rate/100 person-years
Original cohort event rate/100 person-years
0
2
4
6
8
10
12


ATRIA
Diagonal
RE-LY event rate/100 person-years
Original cohort event rate/100 person-years
0
2
4
6
8
10
12

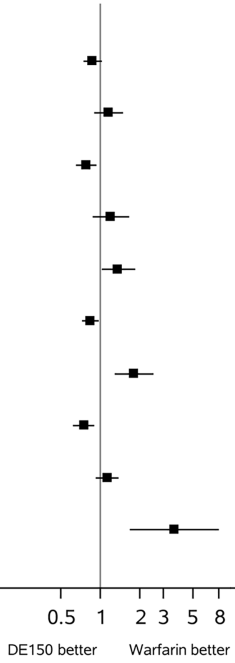

HEMORR2HAGES
Diagonal
RE-LY event rate/100 person-years
Original cohort event rate/100 person-years
0
2
4
6
8
10
12


A
Score
Value
No at risk
No of events
p-value interaction DE vs W
HAS-BLED, DE110
0 411 4
1 2128 89
2 2357 151
3 923 89
≥4 196 14
0.50
HAS-BLED, DE150
0 464 8
1 2130 85
2 2335 179
3 962 109
≥4 185 28
0.0122
HAS-BLED, W
0 409 11
1 2071 112
2 2379 184
3 972 97
≥4 191 22
ORBIT, DE110
0 1241 20
1 2006 72
2 1480 111
3 780 71
4 366 51
5 142 22
0.0051
ORBIT, DE150
0 1264 22
1 1966 89
2 1508 108
3 835 90
4 362 67
5 141 33
<.0001
ORBIT, W
0 1175 36
1 2036 140
2 1527 102
3 756 68
4 376 55
5 152 25
ATRIA, DE110
0 3116 101
1 130 3
2 1825 141
3 510 39
≥4 434 63
0.0047
ATRIA, DE150
0 3069 107
1 139 3
2 1919 150
3 478 58
≥4 471 91
<.0001
ATRIA, W
0 3061 161
1 150 8
2 1881 150
3 469 55
≥4 461 52
HEMORR2HAGES, DE110
0 2020 67
1 2284 126
2 1214 95
3 407 51
≥4 90 8
0.0612
HEMORR2HAGES, DE150
0 1989 57
1 2302 138
2 1274 130
3 396 55
≥4 115 20
<.0001
HEMORR2HAGES, W
0 1976 90
1 2303 166
2 1234 122
3 407 40
≥4 102 8
0 5 10 15 20
Incidence rate (95%CI)
B
Score
Value
No at risk
No of LTB events
p-value interaction DE vs W
HAS-BLED, DE110
0 411 1
1 2128 40
2 2357 68
3 923 37
≥4 196 5
0.91
HAS-BLED, DE150
0 464 4
1 2130 36
2 2335 75
3 962 56
≥4 185 12
0.0428
HAS-BLED, W
0 409 6
1 2071 61
2 2379 91
3 972 48
≥4 191 15
ORBIT, DE110
0 1241 9
1 2006 29
2 1480 58
3 780 29
4 366 16
5 142 10
0.12
ORBIT, DE150
0 1264 8
1 1966 34
2 1508 55
3 835 40
4 362 33
5 141 13
0.0008
ORBIT, W
0 1175 19
1 2036 70
2 1527 55
3 756 40
4 376 28
5 152 9
ATRIA, DE110
0 3116 46
1 130 0
2 1825 66
3 510 15
≥4 434 24
0.12
ATRIA, DE150
0 3069 45
1 139 0
2 1919 70
3 478 30
≥4 471 38
0.0004
ATRIA, W
0 3061 83
1 150 5
2 1881 79
3 469 32
≥4 461 22
HEMORR2HAGES, DE110
0 2020 30
1 2284 53
2 1214 41
3 407 25
≥4 90 2
0.21
HEMORR2HAGES, DE150
0 1989 21
1 2302 69
2 1274 56
3 396 25
≥4 115 12
0.0020
HEMORR2HAGES, W
0 1976 41
1 2303 99
2 1234 55
3 407 21
≥4 102 5
0 2 4 6 8
Incidence rate (95%CI)
C
Score
Value
No at risk
No of ICH events
p-value interaction DE vs W
HAS-BLED, DE110
0 411 0
1 2128 12
2 2357 10
3 923 5
≥4 196 0
0.32
HAS-BLED, DE150
0 464 0
1 2130 12
2 2335 18
3 962 5
≥4 185 4
0.59
HAS-BLED, W
0 409 2
1 2071 30
2 2379 35
3 972 19
≥4 191 5
ORBIT, DE110
0 1241 1
1 2006 7
2 1480 12
3 780 6
4 366 1
5 142 0
0.76
ORBIT, DE150
0 1264 4
1 1966 12
2 1508 9
3 835 6
4 362 5
5 141 3
0.76
ORBIT, W
0 1175 4
1 2036 35
2 1527 22
3 756 15
4 376 12
5 152 3
ATRIA, DE110
0 3116 9
1 130 0
2 1825 14
3 510 2
≥4 434 2
0.80
ATRIA, DE150
0 3069 15
1 139 0
2 1919 14
3 478 4
≥4 471 6
0.57
ATRIA, W
0 3061 35
1 150 2
2 1881 38
3 469 8
≥4 461 8
HEMORR2HAGES, DE110
0 2020 7
1 2284 12
2 1214 6
3 407 2
≥4 90 0
0.30
HEMORR2HAGES, DE150
0 1989 8
1 2302 14
2 1274 9
3 396 5
≥4 115 3
0.49
HEMORR2HAGES, W
0 1976 19
1 2303 36
2 1234 23
3 407 10
≥4 102 3
0 1 2 3
Incidence rate (95%CI)

Score	Category	DE110 Events(%/yr)	Warfarin Events(%/yr)	HR (95% CI)	p-value interaction
HAS-BLED	0-2	244 (2.51)	307 (3.19)	0.78 (0.66-0.93)	0.51
	>2	103 (4.74)	119 (5.48)	0.87 (0.67-1.13)	
ORBIT	0-2	203 (2.15)	278 (2.96)	0.72 (0.60-0.87)	0.17
	3	71 (4.72)	68 (4.77)	1.00 (0.71-1.39)	
	>3	73 (7.53)	80 (8.21)	0.92 (0.67-1.26)	
ATRIA	<4	284 (2.57)	374 (3.42)	0.75 (0.64-0.87)	0.0097
	≥4	63 (7.54)	52 (6.04)	1.26 (0.87-1.82)	
HEMORR2HAGES	0-1	193 (2.26)	256 (3.04)	0.74 (0.61-0.89)	0.34
	2-3	146 (4.59)	162 (5.08)	0.90 (0.72-1.12)	
	>3	8 (4.61)	8 (4.15)	1.12 (0.42-2.99)	



Score	Category	DE150 Events(%/yr)	Warfarin Events(%/yr)	HR (95% CI)	p-value interaction
HAS-BLED	0-2	272 (2.77)	307 (3.19)	0.87 (0.74-1.02)	0.0607
	>2	137 (6.20)	119 (5.48)	1.15 (0.90-1.47)	
ORBIT	0-2	219 (2.31)	278 (2.96)	0.78 (0.65-0.93)	0.0019
	3	90 (5.59)	68 (4.77)	1.19 (0.87-1.63)	
	>3	100 (10.71)	80 (8.21)	1.36 (1.01-1.82)	
ATRIA	<4	318 (2.85)	374 (3.42)	0.83 (0.72-0.97)	<.0001
	≥4	91 (10.28)	52 (6.04)	1.80 (1.28-2.52)	
HEMORR2HAGES	0-1	195 (2.29)	256 (3.04)	0.75 (0.62-0.90)	<.0001
	2-3	185 (5.59)	162 (5.08)	1.12 (0.91-1.38)	
	>3	29 (13.79)	8 (4.15)	3.63 (1.66-7.95)	



Comparison of Bleeding Risk Scores in Patients with Atrial Fibrillation:

Insights from the RE-LY Trial

Supplementary Materials

Table of Contents

Supplementary Methods

Definition and Categorization of the Bleeding Risk Scores

The HAS-BLED score was developed in 2010(1), from data originating from the Euro Heart Survey on atrial fibrillation (AF), an observational study by the European Society of Cardiology(2). One point each was allocated for the presence of uncontrolled hypertension (systolic blood pressure [BP] >160 mmHg), impaired renal or liver function, history of stroke, history of bleeding (or condition predisposing to bleeding), labile international normalized ration (INR), elderly (age>65 years), concomitant use of aspirin or non-steroidal anti-inflammatory drugs and alcohol consumption (more than 20 units a week). The "impaired renal function" variable was considered for a creatinine clearance <60 ml/min according the Cockroft-Gault formula. The "impaired liver function" was defined as chronic hepatic disease (*e.g.*, cirrhosis) or biochemical evidence of significant hepatic derangement (*e.g.*, bilirubin > 2 × upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase > 3 × upper limit normal). A condition predisposing to bleeding was considered for a haemoglobin level <13 g/dL in males or <12 g/dL in females. Labile INR was defined according the baseline question as part of original study case report form (CRF) "Has patient had difficulty with INR control?". A sensitivity analysis was also performed using an alternative definition for labile INR, according INR value at randomization. For the sensitivity analysis one point was assigned as an INR value above 3 or an INR value below 2, in relation to the vitamin K antagonist discontinuation timing. An HAS-BLED score ≤2 was categorized as "low risk", while HAS-BLED score ≥3 was categorised as "high risk"(3).

The ORBIT score was developed from the "Outcomes registry for better informed treatment of atrial fibrillation" study cohort(4, 5), and calculated as follows: 1 point each for age older than 74, insufficient kidney function (defined as a creatinine clearance <60 ml/min according Cockcroft-Gault) and treatment with any antiplatelet drug, while 2 points were assigned for a clinical history of

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). An ORBIT score ≤2 was categorised as "low risk", an ORBIT score equal to 3 as "intermediate risk", while a total score of 4 or higher as "high risk".

The ATRIA score was developed in 2011 from a derivation cohort of the "Anticoagulation and Risk Factors in Atrial Fibrillation" study, a large nationwide observational cohort on AF patients among the general population(6). According the original design, three points were assigned for the presence of anaemia or concomitant diagnosis of a severe renal disease (creatinine clearance <30 ml/min), 2 points for age ≥75 years and one point for a positive clinical history of bleeding or diagnosis of hypertension. Anemia was considered for haemoglobin level <13 g/dL in males or <12 g/dL in females. A total score <4 points was categorized as "low risk", a score of 4 "intermediate risk", while a score >4 was defined as "high risk".

The HEMORR$_2$HAGES score was developed in 2006 and derived from the "National Registry of Atrial Fibrillation", comprised of AF patients within a Medicare program(7). The original model allocated one point for the following: hepatic or renal disease, ethanol abuse, malignancy, older age (≥75 years), reduced platelet count or function, uncontrolled hypertension, anaemia, genetic factors, excessive fall risk, history of stroke. Two points were assigned for a positive bleeding history. We considered "alcohol abuse" as the consumption of >20 units of alcohol per week. Hepatic and renal disease, uncontrolled hypertension and anemia were defined as detailed above. Excessive fall risk was considered according the baseline question in CRF "Has the patient had a fall within the last year?". Furthermore, due to the absence of data about genetic factors, this item was not considered for the score calculation. Patients were categorized as "low risk" for score of 0-1, "intermediate risk" was defined for a score of 2-3, while a score ≥4 was defined as "high risk".

Table S1: Baseline Characteristics According to Randomized Treatment and Major Bleeding Occurrence

	Dabigatran 110		**Dabigatran 150**		**Warfarin**	
	Major Bleeding		**Major Bleeding**		**Major Bleeding**	
	No N=5668	**Yes** N=347	**No** N=5667	**Yes** N=409	**No** N=5596	**Yes** N=426
Age, (*years*) median [IQR]	72 [66-77]	76 [71-80]	72 [66.0-77.0]	77 [71-81]	72 [67-77]	74 [69-79]
Age≥75 years, n (%)	2141 (37.8)	208 (59.9)	2214 (39.1)	252 (61.6)	2213 (39.5)	210 (49.3)
Female, n (%)	2031 (35.8)	118 (34.0)	2090 (36.4)	146 (35.7)	2064 (36.9)	149 (35.0)
Sitting SBP, (*mmHg*) median [IQR] *(18086)**	130 [120-140]	130 [118-140]	130 [120-140]	130 [119-140]	130 [120-140]	130 [120-140]
CrCL, (*mL/min*), median [IQR] *(17375)**	69.5 [53.8-88.1]	56.4 [44.4-72.8]	68.5 [53.5-87.2]	58.9 [45.5-76.5]	69.2 [54.3-87.2]	62.0 [49.0-77.0]
Hypertension, n (%)	4463 (78.8)	275 (79.3)	4449 (78.5)	346 (84.6)	4401 (78.6)	349 (81.9)
Diabetes Mellitus, n (%)	1302 (23.0)	107 (30.8)	1271 (22.4)	131 (32.0)	1294 (23.1)	116 (27.2)
Coronary Artery Disease n (%)	1523 (26.9)	138 (39.8)	1555 (27.4)	155 (28.1)	1507 (26.9)	156 (36.6)
Previous Stroke/SEE/TIA, n (%)	1236 (21.8)	72 (20.7)	1243 (21.9)	115 (28.1)	1185 (21.2)	102 (23.9)

Heart Failure, n (%)	1537 (27.1)	104 (30.0)	1542 (27.2)	98 (24.0)	1500 (26.8)	123 (28.9)
Previous VKA Use, n (%)						
Experienced	2840 (50.1)	168 (48.4)	2831 (50.0)	216 (52.8)	2710 (48.4)	219 (51.4)
Naive	2826 (49.9)	179 (51.6)	2835 (50.0)	193 (47.2)	2886 (51.6)	207 (48.6)
CrCL Category, n (%) *(17375)**						
<50 mL/min	1028 (18.9)	123 (36.6)	1064 (19.5)	124 (31.4)	968 (18.1)	113 (27.1)
50-79 mL/min	2558 (47.1)	156 (46.4)	2589 (47.5)	188 (47.6)	2596 (48.6)	210 (50.4)
≥80 mL/min	1842 (33.9)	57 (17.0)	1799 (33.0)	83 (21.0)	1783 (33.3)	94 (22.5)
History of Fall, n (%)	628 (11.1)	58 (16.7)	604 (10.7)	89 (21.8)	610 (10.9)	58 (13.6)
Anemia, n (%)	729 (12.9)	97 (28.0)	699 (12.3)	133 (32.5)	718 (12.8)	97 (22.8)
Malignancy, n (%)	565 (10.0)	48 (13.8)	582 (10.3)	69 (16.9)	567 (10.1)	54 (12.7)
Concomitant ASA, n (%)	2840 (50.1)	168 (48.4)	2150 (37.9)	188 (46.0)	2231 (39.9)	200 (46.9)
Statins, n (%)	2532 (44.7)	170 (49.0)	2477 (43.7)	205 (50.1)	2472 (44.2)	201 (47.2)
H2 Blockers, n (%)	221 (3.9)	18 (5.2)	228 (4.0)	29 (7.1)	244 (4.4)	18 (4.2)
ACEi/ARB, n (%)	3749 (66.1)	238 (68.6)	3778 (66.7)	284 (69.4)	3651 (65.2)	283 (66.4)

Amiodarone, n (%)	610 (10.8)	37 (10.8)	632 (11.1)	40 (10.0)	622 (11.1)	35 (8.3)
PPI, n (%)	786 (13.9)	61 (17.6)	790 (13.9)	88 (21.5)	766 (13.7)	76 (17.8)
$CHADS_2$, median [IQR]	2 [1-3]	2 [2-3]	2 [1-3]	2 [2-3]	2 [1-3]	2 [2-3]

Legends: *total number of patients with available data about the covariate; ACEi= angiotensin converting enzyme inhibitor; ARBs= angiotensin receptor blocker; ASA= acetylsalicylic acid; CrCl= creatinine clearance; IQR= interquartile range; PPI= proton pump inhibitor; SBP= systolic blood pressure; SEE= systemic embolic event; TIA= transient ischemic attack; VKA= vitamin K antagonist.

Table S2: Bleeding Risk Prediction Scores According Randomized Treatment and Major Bleeding Occurrence

	Dabigatran 110		**Dabigatran 150**		**W**		**P_{int}**	
	Major Bleeding		**Major Bleeding**		**Major Bleeding**		**DE110 vs. W**	**DE150 vs. W**
	No N=5668	**Yes** N=347	**No** N=5667	**Yes** N=409	**No** N=5596	**Yes** N=426		
HAS-BLED, median [IQR]	2 [1-2]	2 [1-3]	2 [1-2]	2 [2-3]	2 [1-2]	2 [1-3]		
HAS-BLED Categories, n (%)							0.5085	0.0607
Low (0-2)	4652 (82.1)	244 (70.3)	4657 (82.2)	272 (66.5)	4552 (81.3)	307 (72.1)		
High (>2)	1016 (17.9)	103 (29.7)	1010 (17.8)	137 (33.5)	1044 (18.7)	119 (27.9)		
ORBIT, median [IQR]	1 [1-2]	2 [1-3]	1 [1-2]	2 [1-3]	1 [1-2]	2 [1-3]		
ORBIT Categories, n (%)							0.1652	0.0019
Low (0-2)	4524 (79.8)	203 (58.5)	4519 (79.7)	219 (53.5)	4460 (79.7)	278 (65.3)		
Intermediate (3)	709 (12.5)	71 (20.5)	745 (13.1)	90 (22.0)	688 (12.3)	68 (16.0)		
High (>3)	435 (7.7)	73 (21.0)	403 (7.1)	100 (24.4)	448 (8.0)	80 (18.8)		

ATRIA, median [IQR]	0 [0-2]	2 [0-3]	0 [0-2]	2 [0-3]	0 [0-2]	2 [0-3]		
ATRIA Categories, n (%)							0.0097	<.0001
Low (0-3)	5297 (93.5)	284 (81.8)	5287 (93.3)	318 (77.8)	5187 (92.7)	374 (87.8)		
Intermediate/High (≥4)	371 (6.5)	63 (18.2)	380 (6.7)	91 (22.2)	409 (7.3)	52 (12.2)		
HEMORR2HAGES, median [IQR]	1 [0-2]	1 [1-2]	1 [0-2]	2 [1-2]	1 [0-2]	1 [1-2]		
HEMORR2HAGES Categories, n (%)							0.3408	<.0001
Low (0-1)	4111 (72.5)	193 (55.6)	4096 (72.3)	195 (47.7)	4023 (71.9)	256 (60.1)		
Intermediate (2-3)	1475 (26.0)	146 (42.1)	1485 (26.2)	185 (45.2)	1479 (26.4)	162 (38.0)		
High (>3)	82 (1.4)	8 (2.3)	86 (1.5)	29 (7.1)	94 (1.7)	8 (1.9)		

Legend: ATRIA= Anticoagulation and Risk Factors in Atrial Fibrillation; HAS-BLED= Hypertension, Abnormal liver/renal function, Stroke, Bleeding, Labile International Normalized Ratio, Elderly, Drugs or alcohol; HEMORR$_2$HAGES= Hepatic or renal disease, Ethanol abuse, Malignancy history, Older (age >75), Reduced platelet count or function, Rebleeding risk, Hypertension, Anaemia, Genetic factors, Excessive fall risk, Stroke history; IQR= interquartile range; ORBIT= Older age, Reduced haemoglobin/haematocrit/anaemia, Bleeding history, Insufficient kidney function, Treatment with platelets; p_{int}= p value for interaction.

Table S3: Treatment Interactions for Bleeding Risk Prediction Scores Categories for Secondary Outcomes*

	Life-Threatening Bleeding				**Intracranial Bleeding**			
	D110 vs. W	**p_{int}**	**D150 vs. W**	**p_{int}**	**D110 vs. W**	**p_{int}**	**D150 vs. W**	**p_{int}**
	HR (95% CI)		HR (95% CI)		HR (95% CI)		HR (95% CI)	
HAS-BLED Categories		0.9118		0.0574		0.3977		0.6925
Low (0-2)	0.68 (0.53-0.87)		0.71 (0.56-0.90)		0.32 (0.20-0.52)		0.44 (0.28-0.67)	
High (>2)	0.66 (0.45-0.98)		1.07 (0.76-1.50)		0.21 (0.08-0.54)		0.37 (0.17-0.79)	
ORBIT Categories		0.9763		0.0266		0.1592		0.7667
Low (0-2)	0.66 (0.51-0.86)		0.66 (0.51-0.86)		0.33 (0.20-0.54)		0.40 (0.25-0.64)	
Intermediate (3)	0.68 (0.42-1.10)		0.88 (0.57-1.37)		0.38 (0.15-0.97)		0.35 (0.14-0.91)	
High (>3)	0.70 (0.43-1.16)		1.31 (0.85-2.02)		0.07 (0.01-0.50)		0.55 (0.23-1.30)	
ATRIA Categories		0.0662		0.0021		0.8510		0.2888
Low (0-3)	0.63 (0.50-0.78)		0.71 (0.58-0.88)		0.30 (0.19-0.46)		0.39 (0.26-0.58)	
Intermediate/High (≥4)	1.12 (0.63-2.00)		1.70 (1.01-2.88)		0.25 (0.05-1.20)		0.72 (0.25-2.09)	

	Life-Threatening Bleeding				Intracranial Bleeding			
	D110 vs. W	**p_{int}**	**D150 vs. W**	**p_{int}**	**D110 vs. W**	**p_{int}**	**D150 vs. W**	**p_{int}**
	HR (95% CI)		HR (95% CI)		HR (95% CI)		HR (95% CI)	
HEMORR$_2$HAGES Categories		0.1523		0.0073		0.3769		0.6169
Low (0-1)	0.58 (0.44-0.76)		0.63 (0.49-0.82)		0.34 (0.20-0.57)		0.39 (0.24-0.65)	
Intermediate (2-3)	0.87 (0.63-1.21)		1.03 (0.76-1.41)		0.24 (0.11-0.52)		0.41 (0.22-0.76)	
High (>3)	0.44 (0.09-2.28)		2.25 (0.79-6.39)		0.00 (0.00-.)		0.92 (0.19-4.54)	

Legend: *See Table S2 for risk scores acronyms; CI= confidence interval; D110= dabigatran 110 mg; D150= dabigatran 150 mg; HR= hazard ratio; p_{int}= p value for interaction; W= warfarin.

Table S4: Sensitivity Analysis for HAS-BLED According Alternative Definition of "Labile INR"

	Major Bleeding						
	Annualized Event Rates			**Treatment Interactions**			
HAS-BLED*	N (%/year)			D110 vs. W		D150 vs. W	
	D110	D150	W	HR (95% CI)	p_{int}	HR (95% CI)	p_{int}
Low (0-2)	235 (2.45)	258 (2.68)	306 (3.24)	0.75 (0.63-0.89)	0.1340	0.83 (0.70-0.98)	0.0050
High (>2)	112 (4.83)	151 (6.28)	120 (5.12)	0.95 (0.74-1.23)		1.25 (0.99-1.59)	

Legend: *See Table 2 for risk score acronym; CI= confidence interval; D110= dabigatran etexilate 110 mg; D150= dabigatran etexilate 150 mg; HR= hazard ratio; p_{int}= p value for interaction; W= warfarin.

Table S5: Sensitivity Analysis of Discriminative Ability for HAS-BLED According Alternative Definition of "Labile INR"

	Major Bleeding			
	C-index (95% CI)			
HAS-BLED*	**Overall**	**Dabigatran 110**	**Dabigatran 150**	**Warfarin**
	0.60 (0.59-0.62)	0.60 (0.58-0.63)	0.62 (0.60-0.65)	0.59 (0.56-0.61)

Legend: *See Table 2 for risk score acronym; CI= confidence interval.

Supplementary References

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