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Original research

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ABSTRACT

Objectives Current international guidelines advocate the application of bleeding risk scores only to identify modifiable risk factors, but not to withhold treatment in patients at high risk of bleeding. VTE-BLEED (ActiVe cancer, male with uncontrolled hyperTension, anaEmia, history of BLeeding, agE and rEnal Dysfunction) is a simple bleeding risk score that predicts major bleeding (MB) in patients with venous thromboembolism, but has never been evaluated in patients with atrial fibrillation (AF). We sought to evaluate VTE-BLEED in patients with AF included in the Randomised Evaluation of Long-term anticoagulant therapY (RE-LY) trial, to assess whether score classes (high vs low bleeding risk) interact with the tested dabigatran doses (150 vs 110 mg twice daily), and to investigate whether dose reductions based on this interaction might help to lower the incidence of the composite outcome MB, stroke/systemic embolism or death.

Methods The score was calculated in the safety population of RE-LY (n=18 040) and recalibrated for AF (AF-adapted VTE-BLEED or AF-BLEED). HRs were calculated to evaluate the score's predictive accuracy for MB. The risk ratios (RRs) for the composite outcome comparing dabigatran 150 and 110 mg twice daily were calculated for the high-risk group.

Results AF-BLEED classified 3534 patients (19.6%) at high bleeding risk, characterised by a 2.9-fold to 3.4-fold higher risk of bleeding than low bleeding risk patients, across the treatment arms. High bleeding risk patients randomised to 110 mg twice daily had a lower incidence of the composite outcome than those randomised to 150 mg twice daily, for an RR of 0.52 (95% CI 0.35 to 0.78). Compared with the label criteria for dose reduction, AF-BLEED identified an additional 11% of patients who might have benefited from dose reduction.

Conclusions AF-BLEED identified patients with AF at high risk of bleeding. Our findings raise the hypothesis that dabigatran 110 mg twice daily might be considered in patients classified as high risk according to the AF-BLEED score. This study provides a basis for future studies to explore safe dose reductions of direct oral anticoagulants in selected patient groups based on bleeding scores.

INTRODUCTION

One of the cornerstones in the management of non-valvular atrial fibrillation (AF) is oral anticoagulation, which prevents the majority of cardioembolic ischaemic strokes and improves survival.[1–3] However, such treatment is accompanied by the risk of (major) bleeding. Several clinical prediction scores have been developed and validated to assess this bleeding risk.[4–7] Because of the net clinical benefit of oral anticoagulation in patients with AF however, current international guidelines advocate application of bleeding risk scores only to identify modifiable risk factors but not to withhold treatment in patients at high risk of bleeding.[8 9] Although well validated, these scores often involve criteria that are difficult to objectify or require laboratory testing for biomarkers or genetic factors, limiting their clinical usefulness. Moreover, whereas existing bleeding risk scores have been evaluated to decide which patients would benefit from anticoagulation[3 10] or would benefit from treatment with a direct oral anticoagulant (DOAC) rather than a vitamin K antagonist (VKA)[11 12] studies that applied such scores to guide DOAC intensity are scarce.[12]

The six-variable VTE-BLEED (ActiVe cancer, male with uncontrolled hyperTension, anaEmia, history of BLeeding, agE and rEnal Dysfunction) is a simple and objective score to predict major bleeding in patients with venous thromboembolism (VTE) on stable, long-term anticoagulation (table 1).[13–16] The score was derived from patients with VTE randomised to treatment with dabigatran in the two RE-COVER trials, and externally validated in various large prospective studies.[13–15 17–19]

In the current study, we aimed to assess its predictive performance for major bleeding in patients with non-valvular AF. Additionally, we aimed to evaluate whether the AF-adapted VTE-BLEED score (or AF-BLEED to avoid confusion) could potentially aid in deciding the optimal dose of dabigatran in patients with a high risk of bleeding.

METHODS

Design of the RE-LY trial

This is a post hoc analysis of the Randomised Evaluation of Long-term anticoagulant therapY (RE-LY) study, of which the design and results have been reported previously.[20 21] The RE-LY study included 18 113 patients with AF who were randomised to receive the direct thrombin inhibitor dabigatran etexilate at two fixed dosages (150 or 110 mg twice daily) or international normalised ratio (INR)-adjusted warfarin (INR target 2.0–3.0). Patients were followed for a median of 2 years for the occurrence of stroke and/or systemic embolism (primary efficacy outcome) and major bleeding (primary safety outcome). VTE-BLEED was designed to predict major bleeding during anticoagulation.

Table 1 The VTE-BLEED score with original definition of the items

Factor	Score
Active cancer*	2
Male with uncontrolled arterial hypertension†	1
Anaemia‡	1.5
History of bleeding§	1.5
Age ≥60 years	1.5
Renal dysfunction¶	1.5
Classification of patients with the VTE-BLEED score	
Low bleeding risk	Total score <2
High bleeding risk	Total score ≥2

*Cancer diagnosed within 6 months before diagnosis of VTE (excluding basal cell or squamous cell carcinoma of the skin), recently recurrent or progressive cancer or any cancer that required anticancer treatment within 6 months before the VTE was diagnosed.
†Males with uncontrolled arterial hypertension were defined by values of systolic blood pressure ≥140 mm Hg at baseline.
‡Haemoglobin <13 g/dL in men or <12 g/dL in women.
§Including prior major or non-major clinically relevant bleeding event, rectal bleeding, frequent nose bleeding or haematuria.
¶The eGRF <60 mL/min defined the presence of renal dysfunction: eGRF was calculated at baseline with the Cockcroft-Gault formula, which include serum creatinine, age and body weight. The VTE-BLEED items 'active cancer' and 'history of bleeding' were not clearly defined in the RE-LY database: 'cancer at baseline' and 'previous bleeding under anticoagulation therapy' were used for the present analysis, respectively.[13]
eGFR, estimated glomerular filtration rate; RE-LY, Randomised Evaluation of Long-term anticoagulant therapY; VTE, venous thromboembolism; VTE-BLEED, ActiVe cancer, male with uncontrolled hyperTension, anaEmia, history of BLeeding, agE and rEnal Dysfunction.

Therefore, the safety cohort of RE-LY (n=18 040) served for data analysis in the current study.

Aim and design of the present study

The primary aim was to test the performance of VTE-BLEED for predicting major bleeding in patients with AF included in the safety population of RE-LY. As patients with AF are considerably different from the patients with VTE in whom the VTE-BLEED score was derived—notably, in age—we adapted the score to optimise its predictive performance in the AF population (AF-adapted VTE-BLEED or AF-BLEED). Both the definition of single score items and the score threshold identifying high-risk patients were adapted based on receiver operating characteristic (ROC) curve analyses and reclassification tables.

Secondary aim was to evaluate the performance of AF-BLEED in clinically relevant patient subcategories, that is, age below versus above 75 years, men versus women, body mass index <30 vs ≥30 kg/m^2 and estimated glomerular filtration rate <30 vs ≥30 mL/min. In addition, we tested its predictive value for ischaemic stroke and/or systemic embolism.

Lastly, we assessed the potential value of AF-BLEED in determining the optimal anticoagulation regime for patients with AF, that is, either of the two doses of dabigatran etexilate, by assessing the difference in the incidence of the composite outcome death, stroke/systemic embolism and major bleeding between the two doses among patients classified as high risk of bleeding. As the current guidelines recommend dose reduction only in patients aged ≥80 years or using verapamil, we assessed whether AF-BLEED can be used to identify additional patients at high risk for bleeding who could benefit from the lower dabigatran dose.[22]

Definitions

The definitions of major bleeding, stroke and systemic embolism are reported in the RE-LY study and are summarised in the online supplementary file. All events were adjudicated by independent investigators unaware of the treatment assignment, as previously reported.[20 21]

Nearly all VTE-BLEED items were available in the RE-LY database in accordance with the definitions used in the derivation study (table 1).[13] For comparison with the proportion of patients classified as high-risk by VTE-BLEED, patients for whom the lower dose of dabigatran etexilate (110 mg twice daily) is currently recommended were defined as those aged ≥80 years or using verapamil, as stated in the drug label.[23]

Statistical methods

Continuous baseline variables were presented as means (SD), categorical variables as proportions (n/N) and percentages (%). To account for missing values, multiple imputation was used. Details on the imputation method are summarised in the online supplementary file. All calculations were repeated in the complete case analysis cohort (online supplementary tables 1 and 2).

The overall prognostic accuracy of VTE-BLEED was evaluated using ROC curve analysis of the ordinal-continuous score (range 0–9 points). The score calibration was assessed by generating the calibration curve and by calculating the slope shrinkage and intercept, its discriminative performance using the C-statistic. The predictive performance of VTE-BLEED was estimated using univariate Cox logistic regression models on the score dichotomised according to several possible thresholds (high risk vs low risk). HRs with corresponding 95% CIs were obtained for the VTE-BLEED high-risk score class in the predefined patient categories and subgroups, with the low-risk class serving as reference. All calculations were repeated with AF-BLEED. Patients were censored at an outcome event, death or predefined maximum follow-up period, whichever came first. All data were analysed using R V.3.6.3 (R Foundation for Statistical Computing, 2020).

Patient and public involvement

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

RESULTS

Patient population

The safety cohort of the RE-LY trial included 18 040 patients, of whom 6059 were randomised to dabigatran 150 mg twice daily, 5983 to dabigatran 150 mg twice daily and 5998 to INR-adjusted warfarin therapy. Discontinuation rates throughout the 2-year follow-up period were 21% for dabigatran 150 mg, 21% for dabigatran 110 mg and 17% for warfarin. This resulted in a median follow-up on active treatment of 674 days (IQR 476–853) in the RE-LY safety cohort, with a median follow-up of 651 days (IQR 462–619), 668 days (IQR 470–625) and 687 days (IQR 485–649), respectively.

Table 2 shows the baseline characteristics of the study population after multiple imputation. Data from the complete case analysis cohort are described in the online supplementary file.

Occurrence of primary study outcomes

Major bleeding occurred in 1014 (5.6%) patients on active treatment. Patients who experienced a major bleeding event

Table 2 Baseline characteristics of 18 040 patients in the safety cohort of the RE-LY study

Variables	n=18 040
Age, mean (SD)	71.4 (8.6)
Male sex, n (%)	11 480 (63.6)
Hypertension, n (%)*	14 221 (78.8)
CrCl, median (IQR)	68.4 (53.4–86.8)
Diabetes mellitus, n (%)	4204 (23.3)
Coronary artery disease, n (%)	5010 (27.8)
Prior stroke, n (%)	3941 (21.8)
Malignancy, n (%)	1880 (10.4)
Hb level (g/dL), median (IQR)	14.2 (13.2–15.2)
Previous bleeding under anticoagulation, n (%)	3533 (19.6)
Previous VKA use, n (%)	12 312 (68.2)
Concomitant aspirin use, n (%)	7153 (39.7)
CHA_2DS_2VASc score, median (IQR)	4 (3–5)

*Systolic blood pressure >140 mm Hg.
CrCl, creatinine clearance; Hb, haemoglobin; RE-LY, Randomised Evaluation of Long-term anticoagulant therapY; VKA, vitamin K antagonist.

were significantly ($p<0.05$) older (75.1 (SD 6.9) vs 71.2 (SD 8.6) years), had lower creatinine clearance (63.6 (SD 23.1) vs 73.5 (SD 28.0) mL/min/1.73 m^2), more coronary artery disease (37.9% vs 27.2%; OR 1.63, 95% CI 1.43 to 1.86), lower haemoglobin levels (13.5 (SD 1.6) vs 14.2 (SD 1.6) g/dL), more concomitant prescription of aspirin (46.4% vs 39.3%; OR 1.34, 95% CI 1.18 to 1.52) and a higher CHA_2DS_2VASc-score (median 4 (IQR 3–5) vs 3.5 (IQR 3–4)). A total of 328 (1.8%) patients experienced a stroke or systemic embolism.

Performance of the original VTE-BLEED score

After imputation of missing data, VTE-BLEED in its original definition was calculated for all patients. The prevalence of the VTE-BLEED score items are summarised in table 3. Notably, compared with patients with VTE in whom the score was derived, patients with AF were older at inclusion, resulting in 90.8% of the RE-LY patients qualifying for the score item 'age ≥60 years'. With high-risk defined as a score ≥2 according to the original VTE-BLEED threshold, 11 556 patients (64.1%) would have been classified as high risk and 6484 patients (35.9%) as low risk.

The absolute incidence of major bleeding was 6.7% in the high-risk group and 3.7% in the low-risk group for an HR of 1.95 (95%CI 1.65 to 2.29). For dabigatran 150 mg, dabigatran 110 mg and warfarin, the HRs (95% CI) were 2.36 (1.79 to 3.10), 2.19 (1.61 to 2.96) and 1.50 (1.17 to 1.92), respectively. The C-statistics for the continuous VTE-BLEED score were 0.64 (range 0.63–0.66), 0.64 (0.63–0.67) and 0.57 (0.56–0.60) for the three treatments arms, respectively. The calibration intercept was 0.020 (range 0.007–0.062) and the calibration slope was 1.007 (0.997–1.022).

Adaptation of the VTE-BLEED score to patients with atrial fibrillation

We adapted the original VTE-BLEED item 'age ≥60 years' for patients with AF because the mean age in this cohort was >15 years greater than in the derivation and validation VTE cohorts, resulting in the assignment of 1 point to 90% of the RE-LY patients. The new item 'age ≥75 years' was chosen based on two considerations: (i) its prevalence (39.9% of the population presented with this criterion, which is comparable to the 41% of the original item in the VTE cohorts) and (ii) its good accuracy (sum of sensitivity and specificity) on ROC analysis for age as single variable. In the RE-LY population, the optimal cut-off for AF-BLEED, based on clinical judgement and absolute rates observed in high-risk versus low-risk patients, was 3 points. Using this threshold, 14 506 patients (80.4%) were classified as 'low risk' and 3534 (19.6%) as 'high risk'.

Table 3 Distribution of the VTE-BLEED items in the study population and risk of major bleeding

Item	Number of patients presenting with the item (%)	Absolute risk during the whole study period, n (%)	HR (95% CI)
Whole population			
Active cancer	1880 (10.4)	140 (7.4)	1.38 (1.15 to 1.65)
Male with uncontrolled hypertension	3621 (20.1)	175 (4.8)	0.81 (0.69 to 0.95)
Anaemia	2415 (13.4)	275 (11.4)	2.75 (2.39 to 3.16)
History of bleeding	3533 (19.6)	225 (6.4)	1.21 (0.93 to 1.56)
Age ≥60 years	16 387 (90.8)	985 (6)	3.50 (2.42 to 5.06)
Age ≥75 years	7205 (39.9)	582 (8.1)	2.18 (1.93 to 2.47)
Renal dysfunction	6490 (36.0)	510 (7.9)	2.01 (1.77 to 2.27)
Dabigatran 110 mg twice daily			
Active cancer	610 (10.2)	35 (5.7)	1.22 (0.86 to 1.74)
Male with uncontrolled hypertension	1196 (20)	58 (4.9)	0.98 (0.74 to 1.31)
Anaemia	804 (13.4)	80 (9.9)	2.67 (2.06 to 3.46)
History of bleeding	1153 (19.3)	66 (5.7)	1.28 (0.88 to 1.84)
Age ≥60 years	5431 (90.8)	284 (5.2)	5.92 (2.45 to 14.33)
Age ≥75 years	2335 (39)	174 (7.5)	2.53 (2.00 to 3.20)
Renal dysfunction	2164 (36.2)	154 (7.1)	2.26 (1.79 to 2.86)
Dabigatran 150 mg twice daily			
Active cancer	650 (10.7)	59 (9.1)	1.65 (1.25 to 2.18)
Male with uncontrolled hypertension	1194 (19.7)	55 (4.6)	0.72 (0.54 to 0.96)
Anaemia	815 (13.5)	114 (13.9)	3.62 (2.89 to 4.53)
History of bleeding	1171 (19.3)	76 (6.5)	1.15 (0.79 to 1.68)
Age ≥60 years	5498 (90.7)	351 (6.4)	9.34 (3.49 to 25.04)
Age ≥75 years	2457 (40.6)	221 (9)	2.68 (2.17 to 3.33)
Renal dysfunction	2191 (36.2)	187 (8.6)	2.22 (1.80 to 2.74)
Warfarin			
Active cancer	620 (10.3)	46 (7.4)	1.23 (0.90 to 1.67)
Male with uncontrolled hypertension	1231 (20.5)	62 (5)	0.76 (0.57 to 0.99)
Anaemia	796 (13.3)	82 (10.2)	2.11 (1.65 to 2.71)
History of bleeding	1210 (20.2)	84 (6.9)	1.19 (0.83 to 1.71)
Age ≥60 years	5458 (91.0)	350 (6.4)	1.71 (1.09 to 2.69)
Age ≥75 years	2413 (40.2)	187 (7.7)	1.60 (1.30 to 1.96)
Renal dysfunction	2136 (35.6)	168 (7.9)	1.65 (1.34 to 2.03)

VTE-BLEED, ActiVe cancer, male with uncontrolled hyperTension, anaEmia, history of BLeeding, agE and rEnal Dysfunction.

Performance of the AF-BLEED score

The absolute incidence of major bleeding during the first 180 days was 3.9% (137/3534) in the high-risk group and 1.5% (212/14 506) in the low-risk group (HR 2.72; 95% CI 2.15 to 3.45; table 4). AF-BLEED consistently predicted major bleeding among predefined patient subcategories. HRs (95% CI) were 3.44 (2.43 to 4.88), 2.92 (1.82 to 4.68) and 1.90 (1.26 to 2.89) for the dabigatran 150 mg, dabigatran 110 mg and warfarin arms, respectively.

Table 4 Performance of the AF-adapted VTE-BLEED score for predicting major bleeding in the whole study population and predefined subcategories

	Major bleeding during the first 180 days			Major bleeding in the whole study period		
	High risk, n/N (%)	Low risk, n/N (%)	HR (95% CI)	High risk, n/N (%)	Low risk, n/N (%)	HR (95% CI)
Whole study population	137/3534 (3.9)	212/14 506 (1.5)	2.72 (2.15 to 3.45)	338/3534 (9.6)	676/14 506 (4.7)	2.25 (1.94 to 2.60)
Dabigatran 110 mg twice daily	33/1166 (2.8)	48/4817 (1)	2.92 (1.82 to 4.68)	106/1166 (9.1)	183/4817 (3.8)	2.62 (2.02 to 3.40)
Dabigatran 150 mg twice daily	66/1192 (5.5)	82/4867 (1.7)	3.44 (2.43 to 4.88)	132/1192 (11)	223/4867 (4.6)	2.67 (2.11 to 3.39)
Warfarin	38/1177 (3.2)	82/4821 (1.7)	1.9 (1.26 to 2.89)	100/1177 (8.5)	270/4821 (5.6)	1.64 (1.28 to 2.10)
Male	89/2382 (3.7)	122/9098 (1.3)	2.88 (2.15 to 3.86)	235/2382 (9.9)	422/9098 (4.6)	2.37 (2.00 to 2.81)
Female	48/1152 (4.1)	90/5408 (1.7)	2.54 (1.73 to 3.74)	103/1152 (8.9)	254/5408 (4.7)	2.03 (1.56 to 2.64)
Age <75 years	12/587 (2)	121/10 248 (1.2)	1.71 (0.89 to 3.28)	39/587 (6.6)	393/10 248 (3.8)	1.86 (1.30 to 2.64)
Age ≥75 years	125/2947 (4.2)	91/4258 (2.1)	2.02 (1.48 to 2.74)	299/2947 (10.2)	283/4258 (6.6)	1.62 (1.34 to 1.96)
BMI <30 kg/m^2	114/2748 (4.2)	118/9020 (1.3)	3.29 (2.49 to 4.34)	276/2748 (10.1)	391/9020 (4.3)	2.55 (2.15 to 3.03)
BMI ≥30 kg/m^2	22/786 (2.8)	94/5486 (1.7)	1.65 (1.00 to 2.71)	62/786 (7.9)	285/5486 (5.2)	1.61 (1.21 to 2.16)

High risk is defined as AF-adapted VTE-BLEED >3.
AF, atrial fibrillation; BMI, body mass index; VTE-BLEED, ActiVe cancer, male with uncontrolled hyperTension, anaEmia, history of BLeeding, agE and rEnal Dysfunction.

The C-statistics for the adapted ordinal-continuous score were 0.65 (range 0.64–0.66), 0.66 (0.65–0.68) and 0.58 (0.57–0.60) for the three treatments arms, respectively. Results from the model calibration comparing predicted versus actual probability for AF-BLEED as an ordinal-continuous score are depicted in figure 1. Figure 2 shows the Kaplan-Meier cumulative hazard curves for bleeding in high-risk and low-risk patients, according to the AF-BLEED score and its threshold of >3 points for the high-risk category. Online supplementary figure 1 shows the Kaplan-Meier cumulative hazard curves in patients stratified by treatment arm.

The incidence of stroke and systemic embolism was 2.2% in the high-risk group and 1.7% in the low-risk group (HR 1.42; 95% CI 1.07 to 1.88), leading to a C-statistic for the ordinal-continuous score of 0.56 (range 0.55–0.57; table 5).

Reduced dabigatran dose in patients with high bleeding risk using the AF-BLEED score

In AF-BLEED high-risk patients, the rate of the composite outcome (death, major bleeding and stroke/systemic embolism) within the first 180 days was 3.19% in patients on dabigatran 110 mg and 5.97% in patients on dabigatran 150 mg, which corresponds to an HR of 0.51 (95%CI 0.34 to 0.78; online supplementary figure 2).

Figure 3 shows the HRs of dabigatran 110 versus 150 mg for the composite outcome at 180 days and in the whole study period in patients classified as high-risk based on various AF-BLEED thresholds, The driver of the observed benefit was a decrease in major bleeding, with a slight increase in thromboembolic events. Whereas the use of dabigatran 110 mg was associated with a lower hazard of developing the composite outcome during the first 180 days of treatment irrespective of the

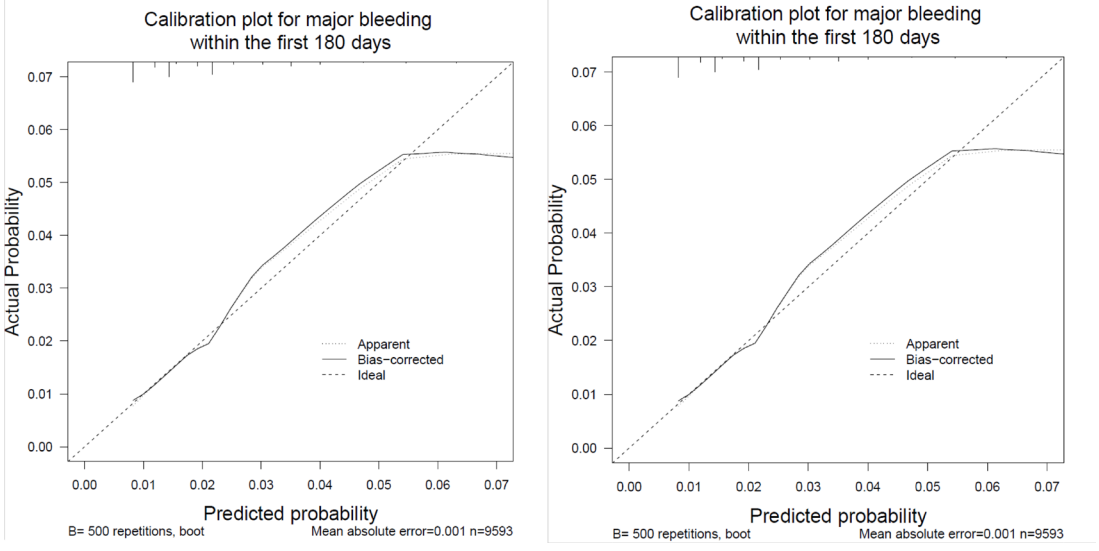

Figure 1 Calibration plots of predicted versus actual probability for AF-BLEED as ordinal score versus bleeding at 180 days (left panel) and bleeding in the whole study period (right panel). The calibration intercept was 0.013 (range −0.020 to 0.042) and the calibration slope was 1.004 (0.992 to 1.014). The score appears to be well calibrated for the range of predicted probability of major bleeding between 1% and 2.5% during the first 180 days and between 3.5% and 5% during the whole study period. For higher values (2.5%–5.5% during the first 180 days and ≥5% during whole study period), the observed probability of the event is slightly higher than the mean predicted probability. For the highest predicted-risk group (above 5.5%), the small size of the subgroups and the much lower observed probability in the whole cohort limit the interpretation of the results.

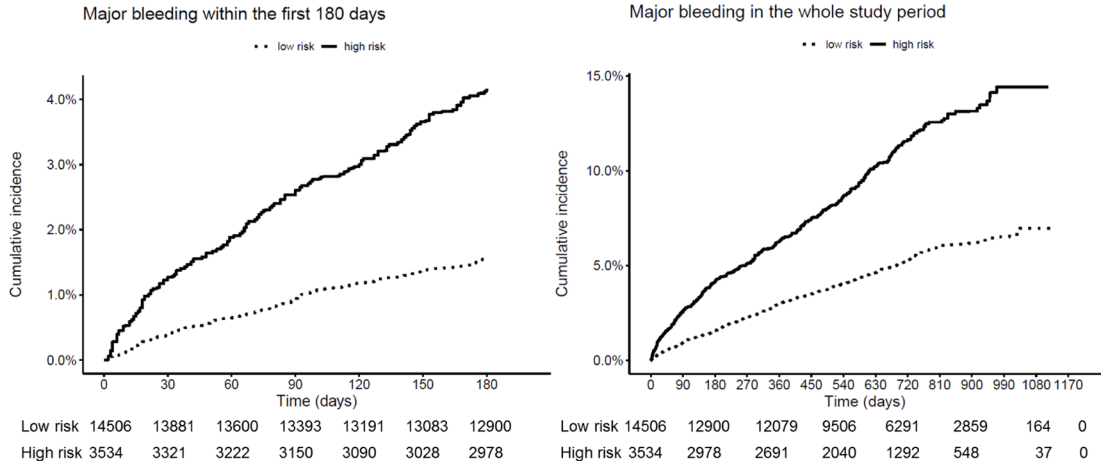

Figure 2 Cumulative incidence of major bleeding in patients classified by the AF-BLEED score. The left panel shows the cumulative incidence of bleeding in the first 180 days. The absolute incidence of major bleeding during the first 180 days was 3.9% (137/3534) in the 'high-risk' group and 1.5% (212/14 506) in the 'low-risk' group (HR 2.72; 95% CI 2.15 to 3.45). The right panel shows the cumulative incidence of bleeding during the whole study period (median follow-up 674 days (IQR 476–853)). The absolute incidence of major bleeding was 9.6% (338/3534) in the 'high-risk' group and 4.7% (676/14 506) in the 'low-risk' group (HR 2.25; 95% CI 1.94 to 2.60).

AF-adapted VTE-BLEED threshold adopted, this positive effect was less pronounced if the whole study period was considered. In the RE-LY cohort, 3867 patients (21.4%) would have been treated with the 110 mg dose of dabigatran according to the drug label.[23] AF-BLEED identified an additional 2000 patients (11% of the total population) who might also have benefited from dabigatran 110 mg. The risk ratio for the occurrence of the composite outcome in the first 180 days for patients treated with the low dose versus high dose according to the label was 0.56 (95% CI 0.36 to 0.87), and for the high-risk patients identified by AF-BLEED 0.52 (95% CI 0.35 to 0.78), respectively.

DISCUSSION

Our results suggest that the AF-BLEED score identifies patients with AF at a twofold to threefold higher risk of major bleeding. This finding was consistent for the overall population as well as for the three treatment arms and across several clinically relevant subgroups, both in the first 6 months of treatment and beyond. Our most important finding was that, compared with the current label of dabigatran, AF-BLEED identified 52% more patients as being at high risk of bleeding who might have benefited from a reduced dose of dabigatran, considering the composite end point of death, major bleeding, stroke or systemic embolism. The absolute risk reduction of this composite end point in patients with an AF-BLEED score >3 points was 2.85% in the initial 6-month treatment period, for an HR of 0.51 (95%CI 0.34 to 0.78).

The C-statistics observed in our study were similar to those calculated in the RE-LY cohort for AF bleeding risk scores, notably the ORBIT score (C-statistic 0.66) and the Hypertension, Abnormal renal and liver function,Stroke, Bleeding, Labile INR, Elderly, Drugs or alcohol (HAS-BLED) score (C-statistic 0.62).[24] We expected a lower discriminative ability of VTE-BLEED in patients with AF due to the intrinsic differences between the AF and VTE population. Compared with patients with VTE in the RE-COVER trial, patients with AF were older (mean age 55 vs 71 years), more frequently had cancer at baseline, and were more likely to be on long-term VKA therapy and aspirin prior to randomisation, most likely due to prior stroke (20%) and known AF.[20] Moreover, patients with uncontrolled hypertension and patients with recent malignancy or radiation therapy were excluded from the RE-LY study.[21] These factors might have contributed to an underestimation of the predictive value of some VTE-BLEED items, reducing the overall performance of the score. While the derivation study of VTE-BLEED indeed yielded higher ORs of bleeding (OR 6.5, 95% CI 2.8 to 15) for high-risk versus low-risk patients with VTE, the HRs and C-statistics found in the validation studies were comparable to those observed in this current analysis.[13 14]

Interestingly, the benefit of dabigatran 110 mg in 'high-risk' AF-BLEED patients was most evident in the first 180 days and least when considering the whole study period. It is likely that a single AF-BLEED assessment at a certain time point does not reflect changes in patient characteristics during long-term follow-up. High-risk patients can return to the low-risk category and vice versa. A perceived high bleeding risk due to incident changes in health could have, for instance, been the reason for discontinuation of anticoagulant treatment in the RE-LY trial, occurring in up to 21% of either dabigatran arm. Unfortunately, precise longitudinal data concerning some of the VTE-BLEED items were not available and, therefore, we were not able to

Table 5 Rate of stroke and systemic embolism in patients classified by the AF-BLEED score

	Stroke and systemic embolism during the first 180 days			Stroke and systemic embolism in the whole study period		
	High risk, n/N (%)	Low risk, n/N (%)	HR (95% CI)	High risk, n/N (%)	Low risk, n/N (%)	HR (95% CI)
Whole study population	23/3534 (0.6)	84/14 506 (0.6)	1.14 (0.69 to 1.90)	78/3534 (2.2)	250/14 506 (1.7)	1.42 (1.07 to 1.88)
Dabigatran 110 mg twice daily	4/1166 (0.4)	36/4817 (0.7)	0.51 (0.18 to 1.45)	26/1166 (2.3)	98/4817 (2.0)	1.23 (0.77 to 1.96)
Dabigatran 150 mg twice daily	6/1192 (0.5)	17/4867 (0.3)	1.60 (0.62 to 4.16)	21/1192 (1.8)	61/4867 (1.2)	1.62 (0.95 to 2.74)
Warfarin	12/1177 (1.0)	32/4821 (0.7)	1.59 (0.73 to 3.47)	30/1177 (2.6)	91/4821 (1.9)	1.47 (0.91 to 2.40)

AF-BLEED, AF-adapted VTE-BLEED.

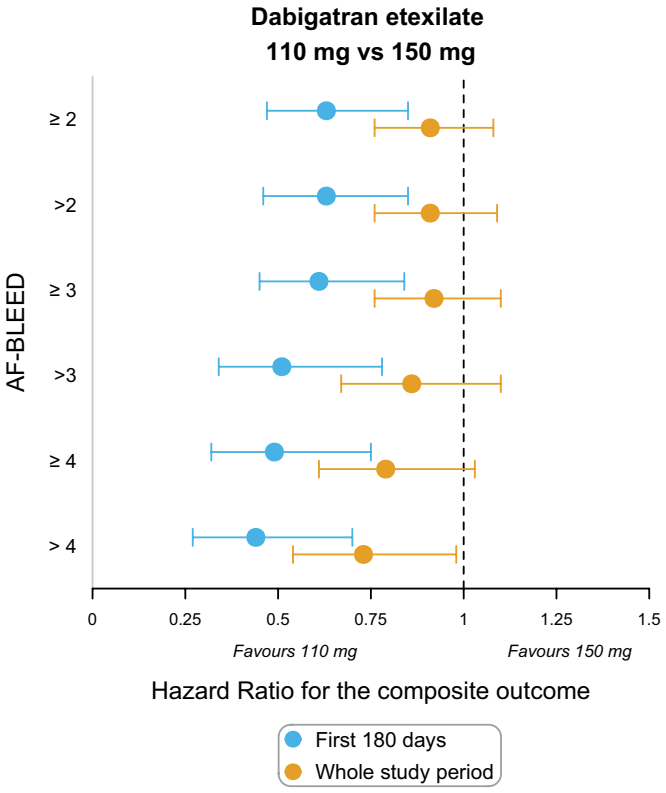

Figure 3 HRs of dabigatran 110 mg versus dabigatran 150 mg for the composite outcome in 'high-risk' AF-BLEED patients. The plot depicts the HR for the composite outcome in 'high-risk' AF-BLEED patients treated with dabigatran etexilate 110 mg versus dabigatran etexilate 150 mg. The use of dabigatran etexilate 110 mg was associated with a lower hazard of developing the composite outcome only during the first 180 days of treatment (blue) and irrespective of the threshold adopted. This effect was absent if the whole study period was considered (yellow).

reassess the performance of the score after the first 6 months of anticoagulation. A second reason explaining these results is that most events occurred during the first months of anticoagulant treatment; therefore, analyses focusing on the period after month 6 could not demonstrate statistically significant differences with the current sample size (figure 3).

Currently, no international AF guideline has provided clear guidance on how to use bleeding and/or stroke risk assessment scores for tailoring anticoagulant treatment or dosage in the individual patient. Although it was proposed in 2012 to use the HAS-BLED score to identify patients at high risk for major bleeding in whom dose reduction of dabigatran should be considered, no studies have validated this concept.[22 25] Recent European and American AF guidelines have limited the application of bleeding risk scores only to identify bleeding risk factors.[8 26] Our findings suggest that AF-BLEED could be used for easy, objective and reproducible identification of patients at high risk of major bleeding who may benefit from the lower dose of dabigatran. Because the benefit of the lower dose of dabigatran was consistent for all tested AF-BLEED thresholds, the score could be used to objectively define a subgroup of patients to be considered for dose reduction rather than to use a list of risk factors that may be present to various degrees in the same individuals. A final benefit of VTE-BLEED would be that the same score may be used in both patients with VTE and AF.

Strengths of this analysis include the use of an existing and validated score rather than the development of a new one, which contributes to the external validity of VTE-BLEED. Also, we were able to use a large, high-quality cohort for our analysis, in which all relevant end points were adjudicated.

STUDY LIMITATIONS

The main limitation of our study is the post hoc design, which resulted in small differences in score item definitions and the exclusion of patients with specific risk factors for bleeding. The score was not derived anew in a cohort of patients with AF and validated in an external cohort; rather, the adaptation of the definition of the score item 'age' as well as the choice of a new threshold were based on the same cohort in which the performance of the score was then tested with consequent overfitting. Moreover, for a substantial proportion of the RE-LY patients, some items of the VTE-BLEED score could not be obtained. Hence, our data should be regarded as hypothesis generating.

CONCLUSION

In the present post hoc analysis, the AF-BLEED score predicted major bleeding in patients with AF included in the RE-LY trial. In patients with high bleeding risk according to AF-BLEED, those treated with the 110 mg twice daily dose of dabigatran had fewer major bleedings, strokes or systemic embolisms than those treated with the 150 mg twice daily dose. Only part of the patients who may potentially benefit from a reduced dose of dabigatran is currently identified by the label. If confirmed

Key messages

What is already known on this subject?

- Although several clinical prediction scores were developed and validated to assess bleeding risk in patients with atrial fibrillation (AF), current international guidelines advocate the application of bleeding risk scores only to identify modifiable risk factors, but not to withhold or alter treatment in patients at high risk of bleeding.

What might this study add?

- The results of this post hoc analysis of the Randomised Evaluation of Long-term anticoagulant therapY study show that AF-adapted VTE-BLEED (ActiVe cancer, male with uncontrolled hyperTension, anaEmia, history of BLeeding, agE and rEnal Dysfunction) identifies patients with AF with a twofold to threefold higher risk of major bleeding than low bleeding risk patients, and raise the hypothesis that these high bleeding risk patients might benefit from a dabigatran dose reduction.
- Compared with the current label of dabigatran, AF-adapted VTE-BLEED could identify 52% more patients who might have benefited from a reduced dose of dabigatran.
- These results provide a basis for future studies to explore safe dose reductions in selected patient groups based on bleeding scores.
- Our study cannot be used to apply dose reduction as standard treatment in high-risk patients.

How might this impact on clinical practice?

- In addition to the dabigatran label, the AF-adapted VTE-BLEED score (or AF-BLEED) could be used to identify patients with AF who might benefit from dose reduction.
- These findings challenges the current view of bleeding risk scores on determining optimal anticoagulation therapy.

by future studies and in patients treated with factor Xa inhibitors for whom different dosages are currently approved, this finding may change the current view on the clinical implications of bleeding risk scores on determining optimal anticoagulation therapy.

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Contributors The authors have reviewed and approved the submission of this manuscript. FAK and MVH were responsible for the conception of the research. GK-BC, LV, SJvdW, SB and FAK drafted the manuscript. LV performed the data analysis. LV, GK-BC, SJvdW, SB and FAK interpreted the data. SK and MVH reviewed and revised the manuscript.

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Competing interests SB reports congress and travel payments from Daiichi-Sankyo and Bayer HealthCare, and lecture honoraria from EKOS Corporation/BTG. SK reports having received consultancy and lecture honoraria from Bayer, Boehringer Ingelheim, Daiichi-Sankyo, MSD and Pfizer—Bristol-Myers Squibb, and institutional grants from Actelion, Bayer, Boehringer Ingelheim, Daiichi-Sankyo and Pfizer—Bristol-Myers Squibb. MVH reports grants from ZonMW Dutch Healthcare Fund, grants and personal fees from Boehringer Ingelheim, grants and personal fees from Pfizer-BMS, grants and personal fees from Bayer Health Care, grants from Aspen, grants and personal fees from Daiichi-Sankyo, outside the submitted work. FAK reports research grants from Bayer, Bristol-Myers Squibb, Boehringer-Ingelheim, Daiichi-Sankyo, MSD and Actelion, the Dutch Heart Foundation and the Dutch Thrombosis Association, outside the submitted work

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval The RE-LY study was approved by all appropriate national regulatory authorities and ethics committees of the participating centres. For the RE-LY study, patients had to provide written informed consent prior to participation. This post hoc analysis of the RE-LY study did not require approval from an ethics committee. The research proposal for this study was submitted to www.clinicalstudydatarequest.com for review and access to anonymised individual patient data from RE-LY was provided.

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