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Full Length Article

External validation of AF-BLEED for predicting major bleeding and for tailoring NOAC dose in AF patients: A post hoc analysis in the ENGAGE AF-TIMI 48

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ABSTRACT

Objective: AF-BLEED, a simple bleeding risk classifier, was found to predict major bleeding (MB) in patients with atrial fibrillation (AF) and identify AF patients at high risk of MB who might potentially benefit from a lower direct oral anticoagulant dose. This post hoc study aimed to externally validate these findings in the ENGAGE AF-TIMI 48 (Effective aNticoaGulation with factor Xa next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction study 48) trial.

Methods: The ENGAGE AF-TIMI 48 trial randomized AF patients to higher-dose edoxaban regimen (HDER 60/30 mg) versus lower-dose edoxaban regimen (LDER 30/15 mg), with prespecified dose reduction criteria. AF-BLEED was calculated in the modified intention-to-treat cohort ($n = 21{,}026$ patients) used for primary outcome analysis. Annualized event rates and hazard ratios (HRs) were obtained for the primary composite outcome (PCO) and its single components (MB, ischemic stroke/systemic embolism and death) to compare LDER 30 mg with HDER 60 mg in both AF-BLEED classes.

Results: AF-BLEED classified 2882 patients (13.7 %) as high-risk, characterized by a two- to three-fold higher MB risk than AF-BLEED classified low-risk patients. AF-BLEED classified high-risk patients randomized to LDER 30 mg demonstrated a 3.3 % reduction in MB at the cost of a 0.5 % increase in ischemic stroke/systemic embolism. LDER 30 mg resulted in a 3.1 % reduction of PCO compared to HDER 60 mg (HR of 0.81; 95%CI 0.65–1.01). Additional to existing dose reduction criteria, another 6 % of patients could potentially benefit of this dose adjustment strategy.

Conclusion: AF-BLEED could identify AF patients to be at high risk of major bleeding. Our findings support the hypothesis that LDER 30 mg might provide a reasonable option in AF patients with legitimate bleeding concerns.

Key messages

What is already known on this topic

- Contemporary atrial fibrillation (AF) guidelines do not recommend the use of bleeding risk classifiers to withhold or alter anticoagulant treatment in patients at high risk of bleeding
- A post hoc analysis of the Randomised Evaluation of Long-term anticoagulant therapY (RE-LY) trial has shown that AF-BLEED, a simple and clinical bleeding risk classifier, could identify AF patients at high risk of bleeding who subsequently might benefit from anticoagulant dose reduction.

What this study adds

- The results of this post hoc analysis of the Effective aNticoaGulation with factor Xa next Generation in Atrial Fibrillation – Thrombolysis in Myocardial Infarction study 48 (ENGAGE AF-TIMI 48) confirm the predictive performance of AF-BLEED in predicting major bleeding, identifying AF patients with a two- to three-fold higher risk of major bleeding.
- In patients deemed at high-risk of major bleeding by AF-BLEED and not meeting any of edoxaban's dose reduction criteria, treatment with a lower edoxaban dose (i.e., 30mg) resulted in fewer major

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bleedings at the expense of a numerically smaller increase in ischaemic stroke and systemic embolism, compared with edoxaban 60mg.

How this study might affect research, practice or policy

- Our findings support the hypothesis that a lower direct oral anticoagulant intensity might provide a reasonable option in AF patients with legitimate bleeding concerns, not addressed by existing dose reduction criteria.

1. Introduction

Several classifiers have been developed to assess bleeding risk in patients with atrial fibrillation (AF) [1–4]. However, their moderate discriminatory performance and lack of clinical implications on anticoagulant treatment have led to limited adoption in contemporary AF guidelines [5–7]. For instance, the European Society of Cardiology recommend the use of a bleeding risk score solely for the identification of (non-)modifiable bleeding risk factors and to identify patients potentially at high risk of bleeding who should be scheduled for frequent follow-up [6]. Even more stringent, the American Heart Association/American College of Cardiology/Heart Rhythm have omitted bleeding risk scores in their guidelines as the evidence for recommendations regarding the clinical utility of bleeding risk scores was considered insufficient [7].

VTE-BLEED, a clinical risk score for predicting major bleeding in patients with venous thromboembolism (VTE) during long-term anticoagulation after the first month from VTE diagnosis, was recently adapted for patients with atrial fibrillation (AF-BLEED) [8,9]. In a post hoc analysis of the RE-LY study, which randomized patients with AF to dabigatran etexilate or warfarin, AF-BLEED identified AF patients at high risk of bleeding, characterized by a 2.9-fold to 3.4-fold higher risk of major bleeding than those classified by AF-BLEED to be at low bleeding risk. Moreover, as a proof of concept, the study showed that AF-BLEED high-risk patients randomized to dabigatran etexilate 110 mg BID had a lower incidence of the composite outcome consisting of major bleeding, stroke/systemic embolism or death, than those randomized to dabigatran 150 mg BID. These findings raise the hypothesis that a bleeding score could be used to guide optimal DOAC dosing, on top of the dose reduction criteria set in current drug labels. This proof of concept provides a perspective for future studies to personalize DOAC prescription and therefore facilitate the development of precision medicine.

The aim of the present study was to externally validate AF-BLEED and the aforementioned findings in the Effective aNticoaGulation with factor Xa next Generation in Atrial Fibrillation – Thrombolysis in Myocardial Infarction study 48 (ENGAGE AF-TIMI 48). We set out to evaluate the performance of AF-BLEED in predicting major bleeding and to evaluate the differences in AF- and anticoagulant-related outcomes between AF-BLEED score classes and allocated anticoagulant treatment (i.e. both edoxaban regimens and warfarin).

2. Methods

2.1. Study population and design

This is a post hoc analysis of the ENGAGE AF-TIMI 48 trial, of which the design and results have been reported previously [10]. In short, the ENGAGE AF-TIMI 48 trial was a randomized controlled trial in which 21,105 AF patients with a $CHADS_2 \geq 2$ were randomized to higher-dose edoxaban regimen (HDER; 60/30 mg), lower-dose edoxaban regimen (LDER; 30/15 mg) or warfarin. For both edoxaban dosing regimens, the dose was halved if any of the following dose reduction criteria were met: estimated creatinine clearance of 30–50/min, a body weight ≤ 60 kg, or concomitant use of verapamil, quinidine or dronedarone (potent P-glycoprotein inhibitors). The analyses were performed in the modified intention-to-treat cohort which excluded patients who did not receive any study drug ($n = 79$), resulting in the inclusion of 21,026 patients. Patients were followed for a median of 2.8 years for the occurrence of stroke and/or systemic embolism (primary efficacy outcome) as well as major bleeding (primary safety outcome).

2.2. Aims of the present study

The aim of this study is to replicate the results of the post hoc analysis performed in the RE-LY trial [9]. In addition to establishing the performance of AF-BLEED in predicting major bleeding in the overall population of the ENGAGE AF-TIMI 48 trial, we also studied its performance in clinically relevant patient subcategories: male/female, age ≥ 75 years, age < 75 years, BMI ≥ 30 kg/m^2 and BMI < 30 kg/m^2. Moreover, the predictive performance of AF-BLEED for ischemic stroke/systemic embolism was tested as well.

Finally, to determine whether patients deemed at high risk of bleeding by AF-BLEED would benefit from a higher or lower dose edoxaban regimen, we evaluated the incidence of AF- and anticoagulant-related outcomes of both randomization arms per AF-BLEED score class, while accounting for dose reduction status.

2.3. Definition of AF-BLEED

The variables of AF-BLEED and their corresponding points were active cancer (2 points), male with uncontrolled arterial hypertension [1], anemia (1.5), history of bleeding (1.5), age ≥ 75 years (1.5) and renal dysfunction (1.5). Specifications of the variables are listed in the Online Supplementary Material. Patients with an AF-BLEED score > 3 points were considered as high-risk for bleeding [9].

Patients with active cancer (i.e. diagnosed within 5 years) were excluded in the ENGAGE AF-TIMI 48 trial. The ENGAGE-AF TIMI-48 study did however collect detailed information on patients with a post-randomization new diagnosis or recurrence of remote cancer. Non-melanoma localized skin cancer, benign tumours and in situ precancerous lesions (e.g., high-grade cervical dysplasia) were not included in the definition of new or recurrent post-randomization malignancies. Therefore, for the AF-BLEED variable 'active cancer', patients were evaluated based on whether they developed cancer during the trial. The specification of the relevant prior bleedings is listed in the Online Supplementary Material.

2.4. Exposure categories

In this study, the following five exposure categories of the ENGAGE AF-TIMI 48 trial were evaluated in an intention-to-treat analysis: (i) randomized to HDER without dose reduction applied (HDER 60 mg), (ii) randomized to HDER with dose reduction applied (HDER 30 mg), (iii) randomized to LDER without dose reduction applied (LDER 30 mg), (iv) randomized to LDER with dose reduction applied (LDER 15 mg), and (v) warfarin.

2.5. Outcomes

The following primary single endpoints were of interest: major bleeding, stroke/systemic embolic events and all-cause death. Subsequently, life-threatening bleeding, non-fatal disabling stroke, fatal bleeding and fatal ischemic stroke were considered. The definitions of the relevant safety and efficacy outcomes are reported in the ENGAGE AF-TIMI 48 trial. All events were adjudicated by independent investigators unaware of the treatment assignment, as previously reported [10].

The following three composite outcomes, in which different weighting methods were applied in balancing ischemic stroke/SE and bleeding complications based on outcome severity, were considered in our analyses: stroke, systemic embolism, major bleeding or death from any cause (i.e., primary composite outcome, which was pre-specified in

the main trial protocol); disabling stroke, life-threatening bleeding or death from any cause; and stroke (i.e., secondary composite outcome), systemic embolism, life-threatening bleeding or death from any cause (i.e., tertiary composite outcome).

For safety outcomes, we applied the on-treatment principle which accounted for bleeding events until 3 days after the last dose. For efficacy and composite outcomes, we applied the first-to-last dose principle, thus including efficacy events such as ischemic stroke or death occurring during prolonged interruptions.

2.6. Statistical methods

Continuous variables were reported with the appropriate measures of central tendency and variability. Categorical variables were presented as proportions (n/N) and percentages (%). Annualized event rates were calculated for all outcomes and were stratified per AF-BLEED risk class and exposure category.

AF-BLEED's predictive performance was assessed using cox regression analyses: hazard ratios (HRs) for major bleeding and ischemic stroke/SEE were calculated for AF-BLEED high-risk patients and in the relevant subgroups, with AF-BLEED low-risk patients as reference.

To evaluate the interaction between the AF-BLEED score classes and the anticoagulant exposure categories, HRs were calculated comparing LDER 30 mg and HDER 60 mg for the single and composite outcomes, in both AF-BLEED risk categories. To assess whether the effect of the intervention differs between the AF-BLEED risk categories, a test for interaction was performed. A p-value of 0.05 was considered statistically significant. All data were analyzed using SAS, version 9.4.

3. Results

3.1. Patient population

The modified intention-to-treat cohort consisted of 21,026 patients, of whom 7012 were randomized to HDER, 7002 to LDER and 7012 to warfarin. Approximately 25 % fulfilled criteria for dose reduction at baseline, resulting in 1776 HDER patients with dose reduction (i.e. HDER 30 mg) and 1774 LDER with dose reduction (i.e. LDER 15 mg; Table 1).

Approximately 13–14 % of the total patient population were classified by AF-BLEED as high risk for bleeding. The most frequently scored AF-BLEED variable was 'age ≥ 75 years' (40 %), followed by renal dysfunction (34 %) and male with uncontrolled arterial hypertension (18 %). The proportion of AF-BLEED high-risk patients differed between those eligible for dose reduction (26–30 %) and those not eligible for dose reduction (9–14 %). Patients eligible for dose reduction were older, had more frequently anemia, prior stroke or TIA and (by definition) renal dysfunction (Online Supplementary Material).

3.2. Performance of AF-BLEED in predicting major bleeding and ischemic stroke/SE

The annualized event rates of major bleeding were 5.7 % and 2.2 % in AF-BLEED high-risk and low-risk patients respectively, which corresponded to a HR of 2.56 (95%CI 2.25–2.92; Table 2). AF-BLEED consistently predicted major bleeding among the predefined patient and treatment subcategories. HRs for HDER, LDER and warfarin were 2.87 (2.31–3.56), 3.02 (2.29–3.97) and 2.12 (1.72–2.60) respectively. When stratified by dose reduction, HRs for HDER 60 mg and HDER 30 mg were 3.81 (2.91–4.98) and 1.96 (1.33–2.89). HRs were 4.01 (2.90–5.53) and 2.04 (1.18–3.53) in LDER 30 mg and LDER 15 mg, respectively.

For ischemic stroke/systemic embolism, the annualized event rates were 2.6 % and 1.7 % for AF-BLEED high- and low-risk patients respectively, resulting in a HR of 1.52 (1.30–1.79; Table 3). The HRs were 1.41 (1.05–1.91), 1.56 (1.20–2.03) and 1.59 (1.21–2.08) for HDER, LDER and warfarin, respectively. However, after stratification by dose reduction, AF-BLEED did not predict ischemic stroke/SE in HDER and LDER. The HRs for HDER 60 mg and HDER 30 mg were 1.29 (0.80–2.07) and 1.11 (0.73–1.69), while HRs of 1.30 (0.86–1.97) and 1.33 (0.93–1.90) were observed for LDER 30 mg and LDER 15 mg, respectively.

Table 1
Baseline characteristics of the modified intention-to-treat cohort of the ENGAGE AF-TIMI 48 study, overall and by treatment arm.

	Complete case population	HDER			LDER			Warfarin
		All HDER	60 mg no dose reduction	30 mg dose reduction applied	All LDER	30 mg no dose reduction	15 mg dose reduction applied	
N =	21,026	7012	5236	1776	7002	5228	1774	7012
Age, mean (SD)	70.6 ± 9.4	70.6 ± 9.5	68.9 ± 9.2	75.7 ± 8.4	70.6 ± 9.3	69.0 ± 9.1	75.4 ± 8.4	70.5 ± 9.4
Male sex, n (%)	13,020 (61.9)	4353 (62.1)	3551 (67.8)	802 (45.2)	4284 (61.2)	3478 (66.5)	806 (45.4)	4383 (62.5)
Treatment duration, median (IQR)	931 (663–1106)	930 (619–1104)	958 (788–1110)	855 (325–1080)	937 (720–1108)	985 (809–1113)	896 (459–1081)	929 (656–1102)
Hypertension, n (%)*	6369 (30.3)	2072 (29.5)	1603 (30.6)	469 (26.4)	2155 (30.8)	1661 (31.8)	494 (27.8)	2142 (30.5)
CrCL, median (IQR)	70 (54–92)	70 (54–92)	79 (64–100)	46 (39–54)	70 (54–92)	79 (64–99)	47 (40–55)	71 (54–92)
Prior stroke or TIA, n (%)	5950 (28.3)	1968 (28.1)	1402 (26.8)	566 (31.9)	1999 (28.5)	1399 (26.8)	600 (33.8)	1983 (28.3)
Hb level (g/dL), median (IQR)	14 (13–15)	14 (13–15)	14 (13–15)	13 (12–14)	14 (13–15)	14 (13–15)	14 (13–15)	14 (13–15)
History of non-ICH^ bleed, n (%)	2077 (9.9)	704 (10.0)	478 (9.1)	226 (12.7)	698 (10.0)	507 (9.7)	191 (10.8)	675 (9.6)
$CHA_2DS_2VASC_2$ score, median (IQR)	4 (3–5)	4 (3–5)	4 (3–5)	5 (4–6)	4 (3–5)	4 (3–5)	5 (4–6)	4 (3–5)
AF-BLEED risk category								
Low bleeding risk (≤3 points)	18,144 (86.3)	6038 (86.1)	4793 (91.5)	1245 (70.1)	6093 (87.0)	4775 (91.3)	1318 (74.3)	6013 (85.8)
High bleeding risk (>3 points)	2882 (13.7)	974 (13.9)	443 (8.5)	531 (29.9)	909 (13.0)	453 (8.7)	456 (25.7)	999 (14.3)

Note: SD = standard deviation, IQR = interquartile range, *Systolic Blood Pressure > 140 mmHg, CrCl = creatinine clearance, Hb = haemoglobin, ICH = intracranial haemorrhage, CHA2DS2VASc score assigns 1 point for congestive heart failure, hypertension, age of 65 to 74 years, diabetes mellitus, vascular disease history, and female sex, and 2 points for age of at least 75 years and prior stroke or transient ischemic attack, HDER = higher-dose edoxaban regimen, LDER = lower-dose edoxaban regimen.

Table 2
Performance of the AF-BLEED score for predicting major bleeding in the complete study population and the separate treatment arms.

	Major bleeding during the complete study period				
	AF-BLEED High risk		AF-BLEED Low risk		HR (95%CI)
	n/N (%)	% of patient/yrs	n/N(%)	% of patient/yrs	
Complete case population	301/2882 (10.4)	5.7	895/18,144 (4.9)	2.2	2.56 (2.25–2.92)
HDER	113/974 (11.6)	6.7	305/6038 (5.1)	2.3	2.87 (2.31–3.56)
60 mg	70/443 (15.8)	8.7	244/4793 (5.1)	2.2	3.81 (2.91–4.98)
30 mg	43/531 (8.1)	4.8	61/1245 (4.9)	2.4	1.96 (1.33–2.89)
LDER	70/909 (7.7)	4.0	184/6093 (3.0)	1.3	3.02 (2.29–3.97)
30 mg	49/453 (10.8)	5.4	151/4775 (3.2)	1.3	4.01 (2.90–5.53)
15 mg	21/456 (4.6)	2.5	33/1318 (2.5)	1.2	2.04 (1.18–3.53)
Warfarin	118/999 (11.8)	6.5	406/6013 (6.8)	3.0	2.12 (1.72–2.60)
Male	215/2020 (10.6)	5.7	565/11,000 (5.1)	2.2	2.48 (2.12–2.90)
Female	86/862 (10.0)	6.0	330/7144 (4.6)	2.1	2.74 (2.16–3.47)
BMI <30 kg/m^2	221/2199 (10.1)	5.5	492/10,318 (4.8)	2.2	2.51 (2.14–2.94)
BMI ≥ 30 kg/m^2	79/673 (11.7)	6.4	400/7762 (5.2)	2.2	2.82 (2.21–3.59)
Age < 75 years	45/309 (14.6)	8.4	524/12,285 (4.3)	1.8	4.43 (3.26–6.03)
Age ≥ 75 years	256/2573 (9.9)	5.4	371/5859 (6.3)	3.0	1.79 (1.52–2.09)

Table 3
Performance of the AF-BLEED score for predicting stroke/SE in the complete study population and the treatment arms.

	Ischemic stroke/SEE during the complete study period				
	AF-BLEED High risk		AF-BLEED Low risk		HR (95%CI)
	n/N (%)	% of patient/yrs	n/N(%)	% of patient/yrs	
Complete case population	185/2882 (6.4)	2.57	826/18,144 (4.6)	1.69	1.52 (1.30–1.79)
HDER	51/974 (5.2)	2.09	242/6038 (4.0)	1.48	1.41 (1.05–1.91)
60 mg	19/443 (4.3)	1.67	170/4793 (3.5)	1.29	1.29 (0.80–2.07)
30 mg	32/531 (6.0)	2.45	72/1245 (5.8)	2.21	1.11 (0.73–1.69)
LDER	68/909 (7.5)	2.98	314/6093 (5.2)	1.91	1.56 (1.20–2.03)
30 mg	25/453 (5.5)	2.14	214/4775 (4.5)	1.64	1.30 (0.86–1.97)
15 mg	43/456 (9.4)	3.87	100/1318 (7.6)	2.92	1.33 (0.93–1.90)
Warfarin	66/999 (6.6)	2.68	270/6013 (4.5)	1.67	1.59 (1.21–2.08)

3.3. Differences in outcome between HDER and LDER across AF-BLEED score classes

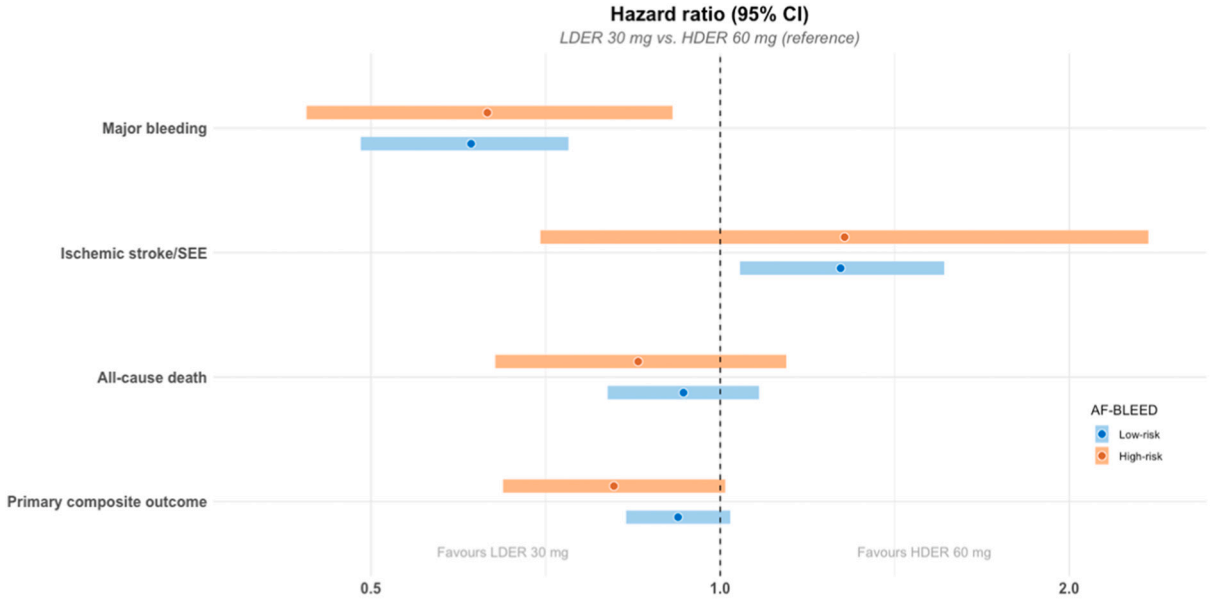
Treatment with LDER resulted in a lower major and life-threatening non-fatal bleeding risk in AF-BLEED high-risk patients when compared with treatment with HDER, with HRs of 0.60 (0.44–0.80) and 0.40 (0.17–0.97), respectively. Conversely, the risk for ischemic stroke/SE increased with the lower dose edoxaban regimen, with a HR of HR 1.44 (1.00–2.07; Online Supplementary Material). For the primary composite outcome, the HR of LDER was 0.92 (0.79–1.08), with HDER as reference.

After considering dose reduction status, high-risk AF-BLEED patients not eligible for dose reduction and treated with LDER 30 mg were characterized by a lower bleeding rate than HDER 60 mg (HR 0.63; 0.44–0.91), but with similar rates for ischemic stroke/SE (HR 1.28; 0.70–2.34) and death (HR 0.85; 0.64–1.14; Fig. 1) when compared to HDER 60 mg. In high-risk AF-BLEED patients, treatment with LDER 30 mg translated to a 3.3 % absolute decrease in major bleeding (8.70 % vs. 5.4 %; a 37 % relative reduction) and an 0.5 % absolute increase in ischemic stroke/SE (1.67 % vs 2.14 %; a 28 % relative increase). A similar trade-off was observed in patients eligible for dose reduction (i.e., HDER 30 mg versus LDER 15 mg, Online Supplementary Material).

For the primary composite outcome, treatment with LDER 30 mg in AF-BLEED high-risk patients led to a non-significant benefit compared to HDER 60 mg (HR 0.81, 95 % CI 0.65–1.01; Fig. 1). Treatment interaction analysis demonstrated no differences in treatment effect for MB, ischemic/stroke, all-cause death and the primary composite outcome between the AF-BLEED score classes (Online Supplementary Material). A higher absolute reduction in outcomes by LDER 30 mg was observed in the AF-BLEED high-risk category than in the low-risk category. For instance, in the AF-BLEED high-risk group, an absolute reduction of 3.08 %/year for the primary composite outcome was observed with LDER 30 mg when compared to HDER 60 mg, while in the low-risk group, a reduction of 0.46 %/year was observed (Fig. 1). This was similar the case for major bleeding (−3.27 %/year vs. -0.88 %/year) and all-cause death (−1.24 %/year vs −0.19 %/year). The differences in outcomes between the other treatment arms across the AF-BLEED score classes are reported in the Online Supplementary Material. Analyses of the other composite outcomes showed similar non-significant trend towards benefit of LDER 30 mg treatment in AF-BLEED high-risk patients, compared with HDER 60 mg. The results of the analyses comparing HDER/LDER versus warfarin are reported in the Online Supplementary Material.

4. Discussion

In this post hoc analysis of the ENGAGE AF-TIMI 48 trial, we have demonstrated that the dichotomized AF-BLEED classifier is able to identify AF patients who are at a two- to three-fold higher risk of major bleeding than their low AF-BLEED score counterparts. Although AF-BLEED was to a lesser extent predictive of ischemic stroke/SE in the separate treatment arms, this was not the case when dose reduction status was considered. As such, AF-BLEED has been validated in two DOAC trials, for three different drug classes (i.e. factor IIa inhibitors, factor Xa inhibitors and vitamin K antagonists) and appears to be applicable in clinically relevant subgroups. As a proof of concept, we have demonstrated the potential utility of AF-BLEED use, as AF patients classified at high-risk for bleeding and treated with LDER 30 mg had a 3 % absolute reduction in major bleeding, at the expense of a 0.5 %



	Outcome	AF-BLEED	Event rate LDER 30 mg (%/year)	Event rate HDER 60 mg (%/year)	Difference
1	Major bleeding	High-risk	5.43	8.70	-3.27
2	Major bleeding	Low-risk	1.34	2.22	-0.88

	Outcome	AF-BLEED	Event rate LDER 30 mg (%/year)	Event rate HDER 60 mg (%/year)	Difference
1	Ischemic stroke/SEE	High-risk	2.14	1.67	+0.47
2	Ischemic stroke/SEE	Low-risk	1.64	1.29	+0.35

	Outcome	AF-BLEED	Event rate LDER 30 mg (%/year)	Event rate HDER 60 mg (%/year)	Difference
1	All-cause death	High-risk	6.95	8.19	-1.24
2	All-cause death	Low-risk	2.60	2.79	-0.19

	Outcome	AF-BLEED	Event rate LDER 30 mg (%/year)	Event rate HDER 60 mg (%/year)	Difference
1	PCO	High-risk	13.03	16.11	-3.08
2	PCO	Low-risk	5.16	5.62	-0.46

Fig. 1. Comparison of LDER 30 mg versus HDER 60 mg per AF-BLEED risk category.

absolute increase in ischemic stroke/SE, when compared with HDER 60 mg.

4.1. Similarities and differences between the current study and the post hoc analysis performed in the RE-LY trial

Our results are in line with a previous post hoc study performed with data from the RE-LY trial, despite some notable differences in patient characteristics and study design [9]. In the current study, fewer patients reported prior bleeding (10 % versus 20 %) or were considered as 'active cancer' patients (5 % versus 10 %). As direct corresponding variables were lacking for the AF-BLEED score items 'active cancer' and 'history of bleeding' in both the RE-LY and the ENGAGE AF-TIMI 48 trial, different surrogates were considered and selected for these score items, based on the available collected trial data. Moreover, multiple imputation was applied to account for missing values in our post hoc analysis of the RE-LY trial. As a result, fewer patients were considered at high-risk for bleeding by AF-BLEED in the ENGAGE AF-TIMI 48 (13.7 %) than in the RE-LY study (19.6 %).

In contrast to the RE-LY trial, the ENGAGE AF-TIMI 48 trial incorporated dose reduction criteria in both HDER and LDER treatment arms after randomization. We found that AF-BLEED's predictive performance for major bleeding depended on dose reduction status. For instance, a four-fold higher risk difference was observed between AF-BLEED score classes in those not eligible for dose reduction, while a two-fold higher risk difference between AF-BLEED score classes was found in those eligible for dose reduction. One likely explanation for this observation is the overlap of 'renal dysfunction' as an AF-BLEED score item and as one of edoxaban dose reduction criteria. A prior post hoc study demonstrated that the 'renal dysfunction' criterion accounted for 60 % of the applied dose reductions in the ENGAGE AF-TIMI 48 trial, and that patients eligible for dose reduction had higher risks of developing major bleeding and ischemic stroke compared to those not eligible [11]. As a result, dose reduced patients with higher stroke and bleeding risks were more likely to be distributed into the AF-BLEED high-risk category. Nonetheless, despite the confounding by the ENGAGE AF-TIMI 48 design, the demonstrated predictive performance of AF-BLEED was in the same order of magnitude as assessed in the RE-LY trial, allowing for the identification of patients at high risk for bleeding in whom frequent follow-up should be considered for targeting modifiable bleeding risk factors.

4.2. Dose reduction in AF-BLEED high-risk patients

As a proof of concept, we assessed whether dose adjustment based on clinical features as assessed by AF-BLEED could reduce major bleeding and the incidences of composite outcomes during follow-up. We have demonstrated that LDER 30 mg resulted in a 3.37 % absolute reduction in major bleeding when compared to HDER 60 mg in AF-BLEED high-risk patients, which translates to a Number-Needed-to-Treat (NNT) of 30. Conversely, LDER 30 mg showed a 0.47 % absolute increase in ischemic stroke/SE, resulting in a Number-Needed-to-Harm (NNH) of 212. In the HDER treatment arm, 443 patients were considered as AF-BLEED high-risk patients and treated with HDER 60 mg. Therefore, an additional 6 % (443/7012) of patients could potentially derive benefit of this dose adjustment strategy.

In the AF-BLEED low-risk group, the absolute reduction in major bleedings that would be prevented by this score-dependent dose reduction strategy was lower: a 0.88 % absolute reduction in major bleeding (NNT 114) at the expense of a 0.35 % absolute and significant increase (HR 1.27 (1.04–1.56); Table S3) in ischemic stroke/SE (NNH 284). In line with this, the potential benefit of LDER 30 mg over HDER 60 mg were, although not significant, estimated to be approximately a 20 % versus an 8 % reduction of the primary composite outcome in the AF-BLEED high- and low-risk group, respectively. Subsequent interaction analysis demonstrated no interaction between AF-BLEED score

classes and DOAC intensity regarding the composite outcome ($p = 0.32$). However, a possible explanation for the failure to detect treatment interaction is underpower, as treatment-subgroup analyses subdivides the data into smaller data sets and thereby requiring inflation of the sample size (i.e., 2 to 16 times higher depending on the magnitude of the treatment interaction) to obtain sufficient power [12–14]. The results of this proof-of-concept study should therefore be perceived as hypothesis-generating.

4.3. Position of current findings in relationship to other studies and contemporary guidelines

Multiple post hoc analyses have been conducted to compare edoxaban and warfarin in different patient subgroups (e.g., including extreme body weight, CHA_2DS_2-VASc score, non-cardiac comorbidities and other subgroups at high-risk for thromboembolic and bleeding events), with the aim to identify patients in whom DOACs would provide therapeutic benefit over VKA [15–17]. However, only few studies have aimed to identify AF patients who could potentially benefit from a lower DOAC dose [18–20].

A recent prespecified post hoc study of the ENGAGE AF-TIMI 48 trial has compared LDER with HDER, utilizing comparable composite outcomes [18]. LDER demonstrated lower incidences of the composite endpoint consisting of stroke/SE, major bleeding and all-cause mortality than HDER, with fewer major bleeding (annualized event rates LDER 1.82 %/y versus HDER 2.87 %/y) counterbalanced by the surplus in ischemic events (annualized event rates LDER 2.04 %/y versus HDER 1.56 %/y). Of note, disabling and fatal strokes were similar between both dosing regiments, while fatal or life-threatening bleedings were fewer with LDER compared with HDER. These findings highlight LDER might be a sensible alternative in AF patients with high bleeding risk. Another study investigating the potential role of a lower DOAC dose was the ELDERCARE-AF randomized controlled trial, which randomized Japanese octogenarians deemed ineligible for oral anticoagulation due to unacceptable high bleeding risk to edoxaban 15 mg once daily versus placebo [21]. This study demonstrated that edoxaban 15 mg once daily reduced the risk of stroke at the cost of a non-significant absolute increase in major bleeding. In AF-BLEED high-risk patients who were already eligible for dose reduction, we observed that LDER 15 mg had lower event rates for major bleeding and a non-significant increase in ischemic stroke/SE compared to HDER 30 mg. However, the high event rates for ischemic stroke in LDER 15 mg (3.87 %/year) warrants caution.

Together with the results of the abovementioned studies, our findings contribute to the hypothesis that in vulnerable patients with legitimate bleeding risk concerns a lower DOAC dose might represent a reasonable approach for stroke prevention. AF-BLEED could be used for easy, objective and reproducible identification of patients at high risk of bleeding and could potentially identify AF patients at high-bleeding risk who may benefit from a lower DOAC intensity.

It should however be stated that current international regulatory authorities do not approve of LDER as the higher trend of stroke/SE events compared with VKA was considered to outweigh the benefit of reduced major non-cerebral bleeding and the net clinical outcome. Moreover, current AF guidelines do not provide recommendations on dose reduction based on bleeding risk scores. Nonetheless, based on the results of post hoc subgroup analyses of the RE-LY trial, European and several international drug agencies except for the U.S. Food and Drug Administration have adopted the recommendation to prescribe dabigatran etexilate 110 mg twice-daily in AF patients ≥80 years in their drug labels [22–26]. It was calculated that a reduced dabigatran dose would result in 10 additional stroke/SE while 99 major bleeding events and 37 intracranial haemorrhage would be avoided [24].

Utilizing composite outcomes require the assumption that the opposing terms carry equal weight in severity and relevance. A direct comparison of major bleeding and ischemic stroke solely based on incidences does not necessarily cover the long-term or functional impact of these adverse outcomes. Although major bleedings in AF is considered to carry some residual long-term risks, the nature of even severe non-intracranial major bleedings are often transient, while AF-related strokes are associated with poorer outcome and long-term functional disability [27–29]. Moreover, patients perspective should be considered in the evaluation of these adverse events, as prior studies have demonstrated that patients could value adverse outcomes differently than physicians [30]. Therefore, future randomized controlled studies on anticoagulation should include functional net clinical benefit outcomes, which encompass outcome severity, residual functional capacity and quality of life measures. This enables physicians and patients to be better informed when deciding whether risk-benefit trade-offs, for instance of anticoagulant tailoring strategies, would likely benefit the individual patient.

5. Study limitations

The multiple stratification per AF-BLEED score classes and dose reduction status resulted in limited statistical power to fully explore the outcomes per stratification category. Moreover, baseline characteristics were not obtained per strata due to expiration of the access rights to the ENGAGE AF-TIMI 48 trial data. However, we do not expect major imbalances in subgroups between AF-BLEED high-risk patients assigned to HDER 60 mg or LDER 30 mg as the spread of the separate AF-BLEED items was comparable between these treatment arms. These items concern important patient characteristics such as age, sex hypertension, anemia, renal function, history of bleeding and cancer. We did not adjust for multiple comparisons, and thus, the chance of a false positive result is possible. As we have performed an intention-to-treat analysis, changes to or permanent discontinuation of anticoagulant treatment were not accounted for. Premature discontinuation of the study drugs, for instance, occurred in approximately 33 % of patients per treatment arm, while dose changes after randomization occurred in >8 % of patients enrolled. Similarly, changes in bleeding risk profile (i.e. AF-BLEED score) were not accounted for during follow-up. The variables chosen as surrogates for certain AF-BLEED score items in both the RE-LY and the ENGAGE AF-TIMI 48 trial did not fully correspond. LDER (i.e. edoxaban 30 mg and 15 mg) and edoxaban 30 mg in patients without at least 1 dose reduction criteria have not been approved by the authoritative drug agencies in Europe and the United States. Finally, the external validity of this trial may be limited as patients had to comply and qualify for a randomized controlled trial, a $CHADS_2$ score of at least 2, and patients with specific bleeding risk factors were excluded from the ENGAGE AF-TIMI 48 trial, thereby limiting the generalizability of current findings.

6. Conclusions

This post hoc analysis of the ENGAGE AF-TIMI 48 trial demonstrated that the AF-BLEED score is able to predict major bleeding in AF patients. In patients deemed at high risk of major bleeding by AF-BLEED and not meeting any of edoxaban's dose reduction criteria, treatment with edoxaban 30 mg showed fewer major bleedings at the expense of a numerically smaller increase in ischemic stroke and systemic embolisms, compared with edoxaban 60 mg. Our findings support the hypothesis that LDER 30 mg might provide a reasonable option in AF patients with legitimate bleeding concerns.

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.

Ethics approval

The ENGAGE AF-TIMI 48 trial was approved by all appropriate national regulatory authorities and ethics committees of the participating centres. For the ENGAGE AF-TIMI 48 trial, patients had to provide written informed consent prior to participation. This post hoc analysis did not required approval from an ethics committee. The research proposal for this study was submitted to vivli.com for review.

CRediT authorship contribution statement

The authors have reviewed and approved the submission of this manuscript. FAK, MVH, GC, SB, LV were responsible for the conception of the research. GC and FAK drafted the manuscript. GC, LV, SB, FAK interpreted the data. MVH, SVK and FAK reviewed and revised the manuscript.

Declaration of competing interest

GC and LV report no competing interests. SB reports congress and travel payments from Daiichi-Sankyo and Bayer HealthCare, and lecture honoraria from EKOS Corporation/BTG. SVK 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.

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Appendix A. Supplementary data

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