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Full Length Article

Predicting clinically relevant bleeding in new-onset atrial fibrillation patients initiating oral anticoagulant therapy: External validation of the AF-BLEED score

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ABSTRACT

Background: Atrial fibrillation/flutter (AF/AFL) is associated with an increased stroke risk, for which oral anticoagulation (OAC) is often indicated. Bleeding risk assessment is crucial in these patients to mitigate bleeding complications, yet AF guidelines do not recommend the use of any bleeding risk score (e.g., HAS-BLED) due to concerns about predictive accuracy. The AF-adapted VTE-BLEED (AF-BLEED) score was developed to predict major bleeding (MB) post-OAC initiation.
Aims: Evaluate the incidence of clinically relevant bleeding, and externally validate the AF-BLEED score in new-onset AF/AFL patients.
Methods: Patients enrolled in the DUTCH-AF registry, who started OAC at diagnosis were studied. AF-BLEED categorized patients as low-risk (score $\leq$ 3) or high-risk (score $>$ 3) for bleeding. Outcomes were first (i) MB and (ii) composite MB and clinically relevant non-major bleeding (CRNMB), with death and OAC discontinuation as competing events. Discrimination (cumulative AUC [AUCt]) was evaluated at 180 days and 2 years.
Results: 4647 patients (AF-BLEED low-risk: 94.0 %) were included. Cumulative MB incidences for low- and high-risk patients were 0.58 % (95 %CI 0.34–0.82 %) and 1.65 % (0.04–3.26 %) at 180 days (p 0.04), and 1.82 % (1.39–2.26 %) and 5.07 % (2.26–7.87 %) at 2 years (p $<$ 0.001), respectively. Cumulative CRNMB/MB incidences for low- and high-risk patients were 1.81 % (1.39–2.24 %) and 4.13 % (1.62–6.65 %) at 180 days (p 0.01), and 6.37 % (5.58–7.16 %) and 9.68 % (5.91–13.45 %) at 2 years (p 0.04), respectively. Discrimination was poor to moderate for both outcomes at both time windows, ranging between 0.51 and 0.62.
Conclusion: Although AF-BLEED was associated with subsequent risk of clinically relevant bleeding, its discriminative ability was poor, limiting the practical utility in its current form.

1. Introduction

The management of atrial fibrillation/flutter (AF/AFL) has traditionally focused on stroke prevention through anticoagulation therapy. The major downside of oral anticoagulant therapy (OAC) is an increased bleeding risk, which could affect treatment adherence and stroke risk as a consequence [1]. Yet, the assessment and management of bleeding risk, a critical consideration in AF patients prescribed OAC, has received comparatively less attention within clinical guidelines and practice [2–4]. This may be due to the notorious difficulty in identifying patients at high or low risk of bleeding. Various bleeding risk scores have been developed to aid in risk assessment (e.g., HAS-BLED, HEMORR$_2$HAGES and ATRIA), but their moderate predictive accuracy has limited their utility [5–8].

Among current risk scores, the AF-BLEED score emerges as a relatively novel tool [9]. AF-BLEED was adapted from the VTE-BLEED score, a score initially developed in a post-hoc analysis of the RE-COVER studies to predict MB in patients with venous thromboembolism (VTE) during the 'stable phase' of OAC (i.e., between 30 days to 6 months after initiation of therapy) [10]. The subsequent AF-BLEED score was developed within a post-hoc analysis of the RE-LY trial, a randomized controlled trial (RCT) comparing dabigatran and warfarin in AF patients [9]. Utilizing the same predictors as those of the VTE-BLEED score, adjustments were made to the age criterion ($\geq$60 years to $\geq$75 years) and the cutoff point for low and high bleeding risk. In both the derivation cohort (RE-LY trial) as well as the external validation study (ENGAGE AF-TIMI 48 trial), AF-BLEED classified high-risk patients experienced higher incidences of major bleeding (MB) as compared to those classified as low risk. Moreover, the authors suggested that AF-BLEED high-risk patients may benefit from reduced rather than full direct oral anticoagulant (DOAC) dosing regimens [9,11].

We aimed to 1) evaluate the incidence of MB and the composite outcome of clinically relevant non-major bleeding (CRNMB) and MB, and 2) externally validate the AF-BLEED risk score to predict these bleeding outcomes, both in a large, Dutch, daily clinical practice cohort of patients with recent-onset AF/AFL initiating OAC.

2. Methods

We followed the recommendations of the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) guideline (Supplementary Material, "TRIPOD Checklist").

2.1. Study design and participants

The design of the DUTCH-AF study has been reported previously [12]. In summary, DUTCH-AF was a prospective, observational, multicenter, nationwide registry including 5933 patients aged $\geq$18 years with newly diagnosed AF or AFL in the Netherlands. Exclusion criteria were: a) mechanical heart valve, b) moderate to severe mitral valve stenosis, c) a life expectancy $<$6 months, or d) a diagnosis of AF/AFL within 14 days post-cardiothoracic surgery. Patients were enrolled between July 2018 and July 3, 2021, from 31 sites; hospitals (secondary and tertiary care), general practices, and thrombosis services (98.3 % of patients were enrolled from hospitals). Follow-up data were collected at 12 and 24 months after inclusion through structured telephone interviews, supplemented by review of patient medical records. Additionally, DUTCH-AF was augmented with pre-existing prospectively collected data from the Netherlands Heart Network, with similar eligibility criteria and follow-up of outcomes [13].

For the aim of the present study, we only included OAC-naive patients in whom OAC (vitamin K antagonist [VKA] or DOAC) was initiated upon diagnosis of AF/AFL. Patients with an unknown date of AF/AFL diagnosis or without availability of follow-up data were excluded.

2.2. Ethical considerations

The DUTCH-AF study protocol was reviewed by the Medical Ethical Committee of the Leiden University Medical Center (LUMC), Leiden, The Netherlands, and it was decided that DUTCH-AF is not subject to the Medical Research Involving Human Subjects Act (WMO), thereby making it exempt from formal ethical approval. The study is registered at the Netherlands Trial Register (NL7464). All participants were informed and provided informed consent for the purpose of data collection.

2.3. AF-BLEED score

The variables included in the score are: 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) [9]. To estimate creatinine clearance, the CKD Epidemiology Collaboration (CKD-EPI) formula was used [14]. Details on the variable definitions are specified in Supplementary Table S1. The authors of the AF-BLEED score defined AF-BLEED low-risk as a score ≤ 3, and AF-BLEED high-risk as a score exceeding 3 points. Model estimates or predictive probabilities were not available.

2.4. Outcomes

2.4.1. Major bleeding and clinically relevant non-major bleeding (CRNMB)

The primary outcome was the first MB following OAC initiation for newly-diagnosed AF/AFL. MB was defined according to the ISTH criteria as an overt bleeding and a) fatal bleeding, and/or b) bleeding in a critical anatomical site (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, intramuscular with compartment syndrome) and/or, c) a decrease in hemoglobin level of ≥1.24 mmol/L (2 g/dL) and/or, d) necessitating transfusion of ≥2 units of packed red blood or whole blood cells [15]. The secondary outcome was the composite outcome of MB and CRNMB. CRNMB was defined according to the ISTH criteria as any bleeding that did not meet the criteria for MB, but required a face-to-face evaluation, medical intervention by a health care professional, or increased level of care (e.g. hospitalization) [15]. Outcome evaluation was performed by research staff at the respective enrollment sites using the predefined MB and CRNMB criteria, with blinding for the AF-BLEED score. No independent adjudication of outcomes was performed.

2.4.2. Discontinuation of oral anticoagulant therapy

Discontinuation of OAC was defined as an interruption of more than 30 days, as documented in the electronic health records or reported by the patient upon telephone interviews [16]. Transitioning to a different type of OAC or brief interruptions (30 days or fewer) were categorized as ongoing use of OAC.

2.5. Statistical analyses

The AF-BLEED score was calculated for each patient eligible for this study using data collected around the time of AF/AFL diagnosis. Follow-up extended from the date of AF/AFL diagnosis to the first outcome of interest (MB or the composite outcome CRNMB/MB), discontinuation of OAC, loss to follow-up, death or the end of the study (final follow-up visit, approximately 2 years after enrollment), whichever came first. Occurrences of death and discontinuation of OAC were treated as competing events. Patients who remained event-free (alive without experiencing the outcome of interest and without discontinuing OAC) until the timeframe of interest (i.e., 180 days/730.5 days) or until the last follow-up in the case of incomplete follow-up, were censored. Incomplete follow-up was defined as patients being followed for less than 180 days or 2-years (i.e. 730.5 days), respectively, despite being event-free during this period.

Results are reported separately for MB and for the composite outcome of MB and CRNMB. We calculated cumulative incidences with 95 %-confidence intervals (95 %CI) of bleeding and the competing events using the non-parametric Aalen-Johansen estimator of the cumulative incidence function (i.e., a multi-state Kaplan-Meier estimator to account for competing risk), and cumulative incidence plots were created [17,18]. Separately, the cumulative incidence of the outcomes of interest within the AF-BLEED categorized low- and high-risk groups were assessed and group differences were evaluated using Gray's test ($p < 0.05$ for significance) [19].

The predictive performance of the AF-BLEED score was evaluated by discrimination (ability to differentiate between patients with and without the outcome of interest) on the intended 180-days and 2-year timeframes, considering time-to-event and competing risks. AF-BLEED was validated as the originally intended dichotomized score (AF-BLEED low- vs high-risk), and as a continuous score (i.e., ranging from 0 to the maximum possible score of 9). We assessed the discrimination using the cumulative area under the receiving operator characteristics curve (AUCt), with the inverse-probability-of-censoring weighting method applied to handle right-censored data [17,20]. An AUCt of 1 represents perfect discrimination, while 0.5 implies random chance (analogous to flipping a coin). Typically, an AUCt of <0.6 is regarded as poor, 0.6–0.75 as moderate/potentially useful, and >0.75 as good/clinically useful [21]. Additionally, AUCt was evaluated over time at monthly intervals up to 2 years. Due to the unavailability of AF-BLEED model estimates and predicted probabilities, a formal calibration was not feasible. Instead, we plotted the non-parametric MB and MB/CRNMB cumulative incidence estimates for the low and high-risk groups against the observed MB incidences in the derivation cohort.

All statistical analyses were performed using R (version 4.1.2.), and relevant packages including *cmprsk*, *survival*, *prodlim*, *riskRegression*, *pec*, and *nephro*.

2.5.1. Missing data

Missing data were handled by complete-case analysis under the assumption of Missing Completely At Random (MCAR). Details regarding missing data mechanisms are provided in the Supplementary Materials, section "Missing data mechanisms".

2.5.2. Sensitivity analyses

Two sensitivity analyses were conducted. First, we evaluated the predictive performance of the AF-BLEED score in subgroups: (i) Patients initially prescribed a DOAC, as prescribing VKA as the first-choice OAC may indicate a specific population with a different bleeding risk; (ii) Patients prescribed standard versus reduced DOAC dosing regimens. Patients considered at high risk of bleeding might be prescribed an (off-label) reduced DOAC dose, potentially resulting in lower bleeding rates, and thereby affecting AF-BLEED's discriminative ability; (iii) Patients with stroke risk factors (i.e., CHA_2DS_2-VASc score ≥ 1 in men, ≥2 in women), as AF-BLEED was derived in a population with an indication for OAC based on stroke risk. Subgroup analyses for patients initially prescribed VKA and those without stroke risk factors were not feasible due to the limited group sizes and the distribution of AF-BLEED low vs high-risk patients.

Second, to assess the association between the AF-BLEED score (continuous/dichotomized) and the occurrence of MB and CRNMB/MB at 180 days and 2 years, we performed univariate Fine-Gray competing risk regression analyses to derive subdistribution hazard ratio's (SHR) and corresponding 95 %CIs. Furthermore, we evaluated the individual variables comprising the AF-BLEED score for their association with MB and CRNMB/MB. The multivariate Fine-Gray subdistribution hazard model was used to evaluate the direction, but not the magnitude, of the effect of the variables on the cumulative incidence of MB and CRNMB/MB, while we used the cause-specific Cox proportional hazard model to quantify the magnitude of the association [22].

3. Results

3.1. Patients

Of the 5933 recent-onset AF/AFL patients included in the registry, 4673 patients newly started OAC at diagnosis. An additional 26 patients were excluded (unknown date of AF/AFL diagnosis or unavailability of follow-up data), leaving 4647 patients for analyses (median age at diagnosis 72 years (Q1–Q3: 65–77), 57.7 % men) (Fig. 1). Patients were included from hospitals (n = 4573, 98.4 %), thrombosis services (n = 41, 0.9 %) and general practices (n = 33, 0.7 %). Of the cohort, 3525

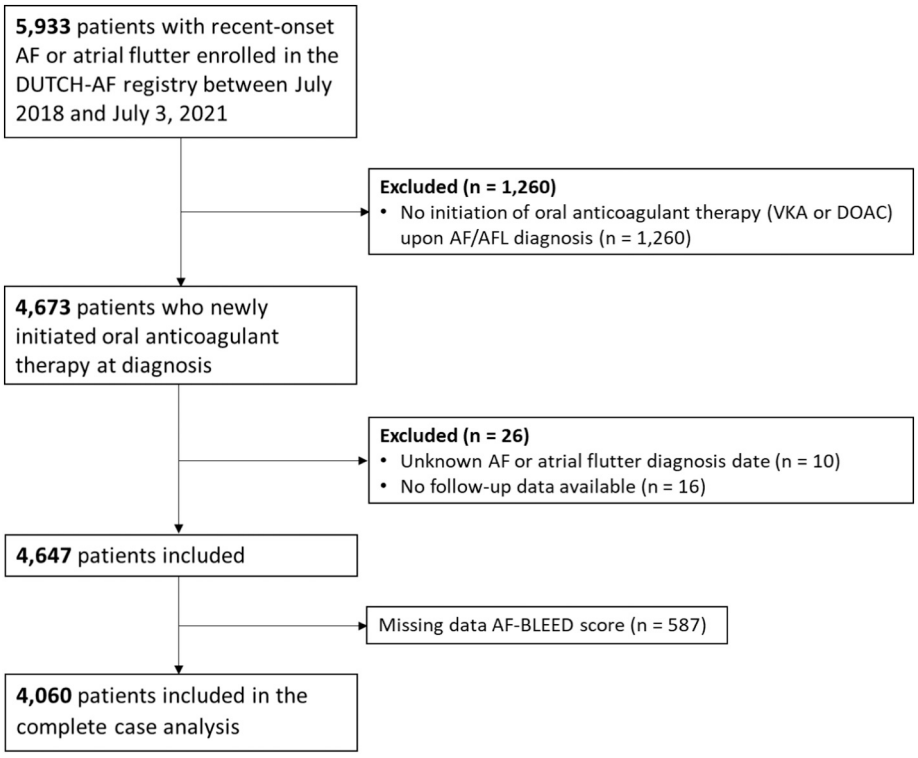

Fig. 1. Flowchart participant inclusion.

patients (75.9 %) were diagnosed with AF, 302 patients (6.5 %) with AFL and 129 patients (2.8 %) had both diagnoses. At diagnosis, DOACs were prescribed in 4432 patients (apixaban: 40.8 %, rivaroxaban: 28.3 %, dabigatran: 18.2 %, edoxaban: 8.0 %) and the remaining 215 patients received VKA (acenocoumarol: 4.0 %, phenprocoumon: 0.6 %) (Table 1). Of the patients prescribed a DOAC, 88.1 % were prescribed a standard dose, 11.5 % a reduced dose and 0.3 % a dose other than recommended by The European Heart Rhythm Association Practical Guide (Supplementary Table S2). In 134 patients (2.9 %), OAC was combined with antiplatelet therapy. A subgroup of the patients (8.2 %) were prescribed OAC in the absence of stroke risk factors (CHA_2DS_2-VASc score 0 in men, $\leq$1 in women), likely related to planned cardioversion or AF/AFL ablation procedures.

3.2. AF-BLEED score

One or more variables of the AF-BLEED score were missing in 587 patients (12.6 %). Therefore, the complete case cohort included 4060 patients (Table 1). The median AF-BLEED score in our cohort was 1 (Q1–Q3: 0–1.5). AF-BLEED classified 3818 patients (94.0 %) as low risk (score $\leq$ 3) and 242 patients (6.0 %) as high risk of bleeding (Fig. 2). Differences in study characteristics and the distribution of predictors between our cohort and the derivation cohort (RE-LY trial) are outlined in Table 1. Notably, fewer patients in our cohort scored positive for the predictors active cancer (3.4 % vs 10.4 %), anemia (4.5 % vs 13.4 %), history of bleeding (0.8 % vs 19.6 %) and renal dysfunction (15.0 % vs 36.0 %) compared to the derivation cohort.

3.3. Primary outcome: major bleeding

3.3.1. Completeness of follow-up

Within the 180-days window, a total of 4033 patients (99.3 %) had complete follow-up. Within the 2-years window (730.5 days), 3320 patients (81.8 %) had complete follow-up and 3717 patients (91.5 %) were followed for at least 22 months or had experienced an event (Supplementary Fig. S1A).

3.3.2. Cumulative incidence of MB and competing events

At 180 days, 26 patients had experienced $\geq$1 MB event, corresponding to a cumulative incidence of 0.64 % (95 %CI 0.40–0.89 %). The incidences among AF-BLEED low- and high-risk patients were 0.58 % (95 %CI 0.34–0.82 %) and 1.65 % (95 %CI 0.04–3.26 %), respectively (Gray's p 0.04). At 2 years, 79 patients had experienced $\geq$1 MB, resulting in a cumulative incidence of 2.02 % (95 %CI 1.58–2.46 %). The incidences among AF-BLEED low- and high- risk patients were 1.82 % (95 %CI 1.39–2.26 %) and 5.07 % (95 %CI 2.26–7.87 %), respectively (Gray's $p < 0.001$) (Fig. 3). The anatomical sites in which MB occurred were mainly gastrointestinal and intracranial (Supplementary Table S3). The first bleeding was fatal in 2 patients (both AF-BLEED low-risk) within the 180-days window and in 7 patients (AF-BLEED low-risk: n = 5, high-risk: n = 2) within the 2-years window.

Within the 180-days timeframe, the cumulative incidences of the competing events mortality and discontinuation of OAC were 0.89 % (0.60–1.18 %) and 4.45 % (3.81–5.08 %), respectively. Within the 2-year window, cumulative incidences of mortality and OAC discontinuation were 4.47 % (3.81–5.12 %) and 8.52 % (7.65–9.38 %), respectively (Fig. 3).

3.3.3. Performance of AF-BLEED score in predicting major bleeding

The cumulative incidences of MB for each AF-bleed sum score are presented in Table 2. The AUCt for the dichotomized AF-BLEED score (low- vs high-risk) was 0.55 (95 %CI 0.48–0.62) at 180 days and 0.55 (95 %CI 0.51–0.59) at 2 years. When assessed as a continuous score, AUCt was 0.59 (95 %CI 0.47–0.71) at 180 days and 0.62 (95 %CI 0.56–0.69) at 2 years. The AUCt remained relatively stable over time (Fig. 4). Comparisons with the MB incidence in the derivation cohort are depicted in Supplementary Fig. S2.

3.4. Secondary outcome: composite outcome CRNMB/MB

3.4.1. Completeness of follow-up

Within the 180-days window, 4033 patients (99.3 %) had complete follow-up and 27 patients had incomplete follow-up. Within the 2-years

Table 1
Clinical characteristics of the included patients from the DUTCH-AF registry, and comparison with AF-BLEED derivation cohort.

	External validation cohort (DUTCH-AF)		Derivation cohort (RE-LY) (n = 18,040), n (%)[a]
	Total (n = 4647), n (%)[a]	Complete case (n = 4060), n (%)[a]	
Type of study	Prospective cohort study		Randomized controlled trial
Age in years, median (Q1–Q3)/mean (±SD)	72 (65–77)	72 (65–77)	71.4 (8.6)
Age ≥ 75 years	1672 (36.0)	1472 (36.3)	7205 (39.9)
Sex, male	2682 (57.7)	2332 (57.4)	11,480 (63.6)
Male patient with uncontrolled hypertension	1231 (26.5)[b]	1107 (27.3)	3621 (20.1)
Prior major bleed	39 (0.8)[b]	34 (0.8)	3533 (19.6)
Anemia	209 (4.5)[b]	194 (4.8)	2415 (13.4)
Renal insufficiency	699 (15.0)[b]	647 (15.9)	6490 (36.0)
Active malignancy	156 (3.4)[b]	139 (3.4)	1880 (10.4)
CHA_2DS_2-VASc score, median (Q1–Q3)	3 (2–4)[b]	3 (2–4)	4 (3–5)
Men with score ≥ 1/ women with score ≥ 2	4250 (91.5)	3719 (91.6)	18,040 (100)
Men with score 0/ women with score ≤ 1	383 (8.2)	329 (8.1)	N.A.
AF-BLEED score, median (Q1–Q3)	1 (0–1.5)[b]	1 (0–1.5)	N.A.
Low risk (score ≤ 3)	3818 (82.3)	3818 (94.0)	4506 (80.4)
High risk (score > 3)	242 (5.2)	242 (6.0)	3534 (19.6)
Diagnosis			
Atrial fibrillation	3525 (75.9)[b]	3064 (75.5)	18,040 (100)
Atrial flutter	302 (6.5)[b]	265 (6.5)	N.A.
Simultaneous atrial fibrillation and flutter	129 (2.8)[b]	115 (2.8)	N.A.
Anticoagulant treatment started at diagnosis			
Direct oral anticoagulant	4432 (95.4)	3872 (95.4)	12,042 (66.8)
Apixaban	1896 (40.8)[b]	1716 (42.3)	N.A.
Dabigatran	846 (18.2)[b]	730 (18.0)	12,042 (66.8)
Edoxaban	370 (8.0)[b]	335 (8.3)	N.A.
Rivaroxaban	1317 (28.3)[b]	1091 (26.9)	N.A.
Vitamin K antagonist	215 (4.6)	188 (4.6)	5998 (33.2)
Acenocoumarol	188 (4.0)	168 (4.1)	N.A.
Phenprocoumon	27 (0.6)	20 (0.5)	N.A.
Warfarin	N.A.	N.A.	5998 (33.2)
Anticoagulation + antiplatelet therapy	134 (2.9)	122 (3.0)	N.A.

[a] Unless otherwise specified.
[b] Missingness: male patient with uncontrolled hypertension n = 95 (2.0 %), prior major bleed n = 65 (1.4 %), anemia n = 349 (7.5 %), renal insufficiency n = 201 (4.3 %), active malignancy n = 26 (0.6 %), CHA_2DS_2-VASc score n = 14 (0.3 %), AF-BLEED score n = 587 (12.6 %), diagnosis n = 691 (14.9 %), type of DOAC started n = 3 (0.06 %).

window (730.5 days), 3350 patients (82.5 %) had complete follow-up and 3720 patients (91.6 %) were followed for at least 22 months or had experienced an event (Supplementary Fig. S1B).

3.4.2. Cumulative incidence of the composite outcome CRNMB/MB and competing events

At 180 days, 79 patients had experienced ≥1 MB or CRNMB, corresponding to a cumulative incidence of 1.95 % (95 %CI 1.53–2.38 %). The incidences among AF-BLEED low- and high-risk patients were 1.81 % (95 %CI 1.39–2.24 %) and 4.13 % (95 %CI 1.62–6.65 %), respectively (Gray's p 0.01). At 2 years, 257 patients had experienced ≥1 MB or CRNMB, resulting in a cumulative incidence of 6.56 % (95 %CI 5.79–7.34 %). Among AF-BLEED low and high risk patients the incidences were 6.37 % (95 %CI 5.58–7.16 %) and 9.68 % (95 %CI 5.91–13.45 %), respectively (Gray's p 0.04) (Fig. 3). CRNMB/MB were mainly gastrointestinal or affecting the skin/subcutaneous tissue (Supplementary Table S3).

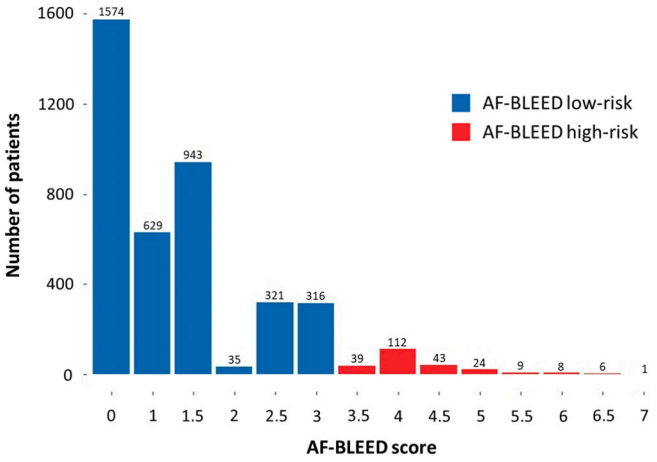

Fig. 2. Distribution of AF-BLEED scores.

Within the 180-days timeframe, the cumulative incidences of the competing events mortality and discontinuation of OAC were 0.89 % (0.60–1.18 %) and 4.22 % (3.60–4.84 %), respectively. Within the 2-year window, cumulative incidences of mortality OAC discontinuation were 4.26 % (3.62–4.90 %) and 8.11 % (7.26–8.96 %), respectively (Fig. 3).

3.4.3. Performance of AF-BLEED score in predicting the composite outcome CRNMB/MB

The cumulative incidences of MB/CRNMB for each AF-bleed sum score are presented in Table 2. The AUCt for AF-BLEED, categorized into low- and high-risk groups, was 0.53 (95 %CI 0.50–0.57) at 180 days and 0.51 (95 %CI 0.50–0.53) at 2 years. When assessed as a discrete score, AUCt was 0.57 (95 %CI 0.50–0.63) at 180 days and 0.57 (95 %CI 0.54–0.61) at 2 years. The AUCt remained relatively stable over time (Fig. 4). Comparison with the MB incidence in the derivation cohort are depicted in Supplementary Fig. S2.

3.5. Sensitivity analyses

3.5.1. Predictive performance of AF-BLEED in subgroups

The predictive performance of AF-BLEED in subgroups for MB and CRNMB/MB was largely in line with that of the main findings, showing consistently poor discrimination (Supplementary Table S4).

3.5.2. Association between AF-BLEED (predictors) and MB and the composite outcome CRNMB/MB

Being classified as AF-BLEED high-risk was associated with a higher incidence of MB at 2 years (SHR 180 days: 2.88, 95 %CI 0.99–8.36; SHR 2 years: 2.85, 95 %CI 1.54–5.28), and with a higher incidence of the composite outcome CRNMB/MB at 180 days and 2 years (SHR 180 days: 2.32, 95 % CI 1.19–4.50; 2 years: 1.58, 95 %CI 1.03–2.43).

When evaluating the predictors included in the AF-BLEED score, only anemia was associated with a higher incidence and risk of MB and the composite outcome CRNMB/MB within 180 days. When evaluating the 2-year window, age ≥ 75 years and anemia were associated with a higher incidence and risk of MB, while age ≥ 75 years, anemia and a history of bleeding were associated with a higher incidence and risk of CRNMB/MB (Supplementary Tables S5 and S6).

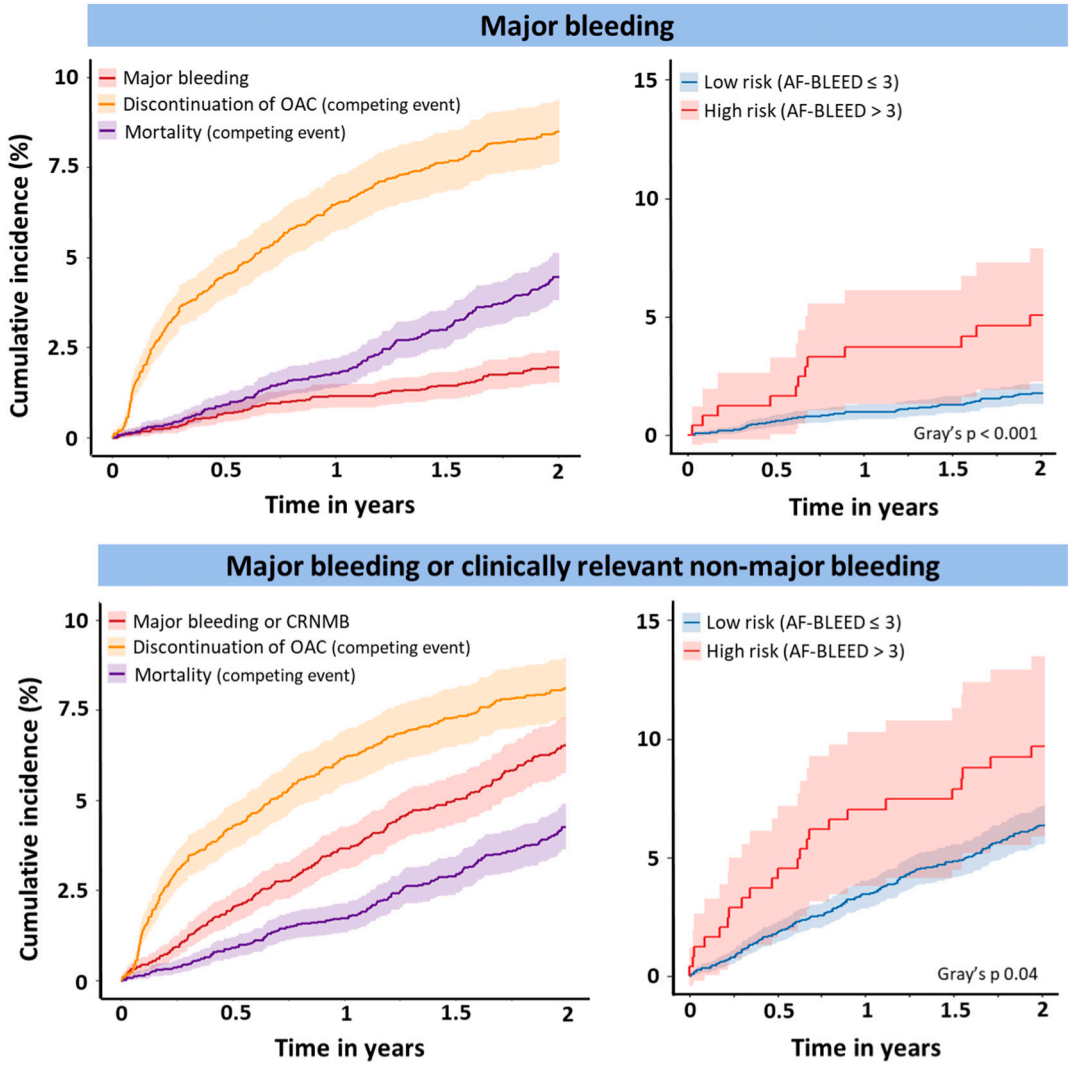

Fig. 3. Cumulative incidences of major bleeding, clinically relevant non-major bleeding (CRNMB) and competing events over time for the entire cohort (left). Cumulative incidences of major bleeding and CRNMB among low- and high-risk groups based on AF-BLEED score (right).

4. Discussion

This study represents the first external validation of the AF-BLEED score's predictive performance for clinically relevant bleeding in a daily clinical practice cohort of recent-onset AF patients treated with OAC. Most patients initiating OAC were classified as low risk by AF-BLEED, consistent with the observed low bleeding rates. High-risk patients experienced higher 180-day and 2-year cumulative bleeding incidences compared to low-risk patients. However, discrimination was poor when using the intended dichotomous risk stratification, with only slight improvement when employing the continuous score.

4.1. Predictive performance of AF-BLEED: comparison with literature

Our findings align with results based on the original derivation cohort (RE-LY trial), which reported poor to moderate predictive performance (c-statistic 0.58–0.66) [9]. AF-BLEED was also externally validated in a post-hoc analysis of the ENGAGE AF-TIMI 48 trial, though the c-statistic was not evaluated [11]. Similar to our findings, both trials observed higher MB incidences among AF-BLEED high-risk versus AF-BLEED low-risk patients, and hypothesized that AF-BLEED high-risk patients may benefit from a reduced OAC regimen [9,11]. Specifically, the ENGAGE AF-TIMI 48 cohort observed a 3.3 % lower MB incidence among AF-BLEED high-risk patients who received a reduced (30 mg) compared to a standard (60 mg) edoxaban dosing regimen, with a 0.5 % increase in ischemic events.

Notably, 2-year MB bleeding incidences were lower in our cohort than in in the RE-LY trial (low-risk: 1.82 % versus 3.7 %; high-risk: 5.07 % versus 6.7 %). As medication adherence is closely monitored in RCTs but likely lower in routine care, reduced OAC-related bleeding may explain this difference. Adherence to OAC will be explored in a separate DUTCH-AF analysis [12]. Additionally, our cohort may have had a better overall health status than the RE-LY and ENGAGE AF-TIMI 48 cohorts. We excluded prior OAC users, and included patients irrespective of stroke risk factors, possibly contributing to differences in predictor distributions (i.e., lower incidences of bleeding history, active cancer, anemia, and renal dysfunction in our cohort). Consequently, only 6.0 % were classified as AF-BLEED high-risk, versus 19.6 % and 13.7 % in the RE-LY and ENGAGE AF-TIMI 48 cohorts, respectively.

AF-BLEED is the first AF bleeding risk score to include active cancer, weighted most heavily based on its predictive value in the VTE-BLEED score [9,10]. Although prior studies in AF patients with cancer support this, only anemia, age $\geq$ 75 years, and prior bleeding were significantly associated with the risk an incidence of clinically relevant bleeding in our cohort [23,24]. This suggests differences in bleeding predictors between VTE and AF. Additionally, VTE-BLEED, developed to predict bleeding during the stable phase of OAC (days 30–180, excluding patients who experienced MB within 30 days), may not cover

Table 2
Cumulative incidence of MB and MB/CRNMB among AF-BLEED sum scores.

AF-BLEED sum score	Cumulative incidence of MB (95 %CI)		Cumulative incidence of MB/CRNMB (95 %CI)	
	180 days	2 years	180 days	2 years
0	0.57 (0.20–0.95)	1.38 (0.79–1.96)	1.79 (1.13–2.44)	5.38 (4.24–6.51)
1	0.16 (0.00–0.47)	1.15 (0.30–2.00)	0.96 (0.19–1.72)	4.44 (2.80–6.09)
1.5	0.64 (0.13 1.15)	2.01 (1.09–2.93)	1.92 (1.04–2.80)	7.13 (5.44–8.82)
2	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)
2.5	0.94 (0.00–2.00)	3.25 (1.26–5.24)	2.19 (0.58–3.80)	8.83 (5.63–12.02)
3	0.95 (0.00–2.03)	3.60 (1.51–5.69)	3.17 (1.24–5.11)	11.19 (7.63–14.75)
3.5	2.56 (0.00–7.59)	5.37 (0.00–12.75)	2.56 (0.00–7.60)	7.95 (0.00–16.73)
4	0.89 (0.00–2.64)	4.62 (0.64–8.59)	4.46 (0.00–8.31)	10.04 (4.37–15.70)
4.5	2.33 (0.00–6.88)	9.30 (0.51–18.10)	6.98 (0.00–14.68)	13.95 (3.46–24.44)
5	4.17 (0.00–12.33)	4.17 (0.00–12.33)	4.17 (0.00–12.33)	4.17 (0.00–12.33)
5.5	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	11.11 (0.00–33.06)
6	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	12.50 (0.00–42.62)
6.5	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)
7	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)
8	NA	NA	NA	NA
9	NA	NA	NA	NA

bleeding dynamics in AF, where there is no initiation phase.

4.2. Importance of bleeding risk assessment and current guidelines

In our predominantly low-risk cohort, the 2-year cumulative MB and CRNMB/MB incidences were 2.02 % and 6.56 %, respectively. Despite AF-BLEED's poor discriminative ability, patients classified as high-risk experienced notable MB or CRNMB/MB incidences within the first two years following OAC initiation (5.07 % and 9.68 %, respectively). Similarly, a Dutch nationwide study using data from Statistics Netherlands (Centraal Bureau voor de Statistiek), including 301,301 newly diagnosed AF patients, reported decreasing but relevant 1-year cumulative MB incidences among patients prescribed OAC (2014: 2.63 % [95 %CI 2.47 %–2.80 %]; 2018: 2.18 % [95 %CI, 2.04 %–2.31 %]) [25]. These findings from daily clinical practice cohorts emphasize the importance of bleeding risk management in AF patients.

Authors of international AF management guidelines (ACC/AHA/ACCP/HRS 2023 and European Society of Cardiology [ESC] 2024) recommend OAC in patients at high risk of stroke, and suggest considering OAC for those at intermediate risk as determined by the CHA_2DS_2-VA(Sc) score, corresponding to an annual ischemic stroke risk of 1.05 % [2–4,26]. Given that our findings indicate that clinically relevant bleeding incidences in AF-BLEED high-risk patients exceed this threshold, the insufficient guidance on bleeding risk management in guidelines is concerning. While encouraging bleeding risk assessment, guidelines caution against withholding OAC solely on this basis. Both guidelines emphasize strict control of modifiable bleeding risk factors, while ESC 2024 additionally advises more frequent monitoring in patients with non-modifiable risks factors. Although the authors of the ESC 2020 guideline suggested HAS-BLED for intensified monitoring in patients at high risk of bleeding, the updated 2024 guideline, like the ACC/AHA/ACCP/HRS 2023 guideline, no longer endorses any specific bleeding risk score due to concerns about their accuracy [2,3,27]. Notably, the CHA_2DS_2-VASc score also showed limited predictive ability, with a pooled C-statistic of 0.64 (95 % CI 0.64–0.65) in a meta-analysis (n = 6,267,728), yet it remains recommended for guiding anticoagulation decisions [28].

Notably, prior studies have shown that currently available bleeding risk scores, including the widely used HAS-BLED score, have poor to moderate predictive ability for MB in AF patients. A meta-analysis of 39 studies, reported moderate discriminative ability of HAS-BLED (pooled C-statistic 0.63; 95 %CI 0.61–0.65), similar to $HEMORR_2HAGES$, ATRIA, ORBIT, GARFIELD-AF, and ABC scores [7]. Furthermore, a French nationwide study (n = 533,044) demonstrated a poor predictive accuracy of HAS-BLED (C-statistic: 0.54; 95 %CI 0.53–0.54), with comparable results observed for $HEMORR_2HAGES$ (0.53; 95 %CI: 0.53–0.54) and ATRIA (0.53; 95 %CI: 0.52–0.54) [29]. Our findings suggest that AF-BLEED performs similarly to these established scores.

4.3. Refining bleeding risk prediction: implications and future directions

With AF prevalence rising, more patients will require anticoagulant therapy, and clinicians will increasingly face the challenge of balancing thromboembolic prevention with bleeding risk. Tailored antithrombotic care may improve both outcomes and quality of life in AF patients. In the following, we provide suggestions for future directions in bleeding risk assessment (Table 3).

At first, we recommend refitting and updating AF-BLEED as

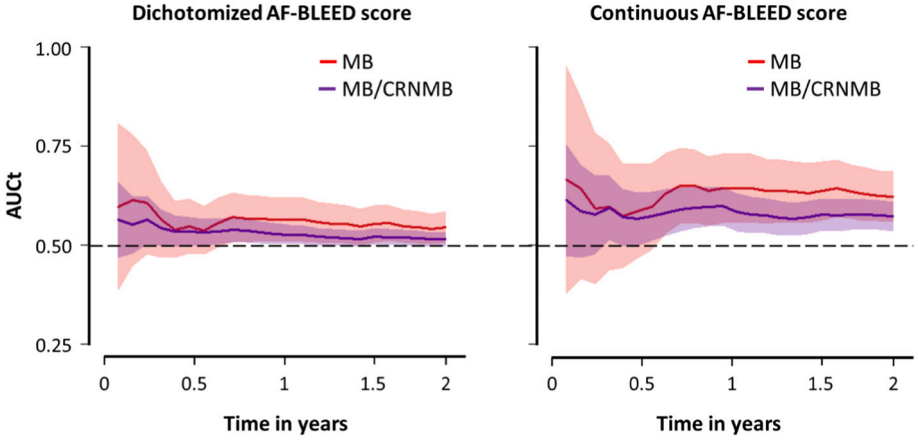

Fig. 4. Visualisation of the discriminative ability (cumulative area under the curve, AUCt, with 95 % confidence intervals) of the AF-BLEED score for major bleeding (MB) and the composite outcome MB and clinically relevant non-major bleeding (CRNMB) over time up to 2 years. The AUCt was evaluated for the intended dichotomized AF-BLEED score (low vs high-risk patients) and the continuous AF-BLEED score.

Table 3
Suggestions for future directions in bleeding risk assessment.

Domain	Current limitation	Future direction
Model performance	Most bleeding risk scores (including AF-BLEED) lack model estimates/formulas to calculate predicted probability	Refit and update existing models (e.g., AF-BLEED) to enable full validation (including calibration) and improve predictive performance
Predictors	Current bleeding risk scores mainly include clinical variables	Evaluate biomarkers associated with bleeding, and investigate their additional value in bleeding risk prediction
Special populations (e.g., frail elderly)	Limited data in vulnerable subgroups	Conduct targeted studies to refine risk prediction and guide therapy in vulnerable subgroups
Integrated risk assessment	Thromboembolic and bleeding risks are currently assessed separately, leading to suboptimal treatment guidance	Develop a combined bleeding and thromboembolic risk score to guide antithrombotic decision making and evaluate applicability in clinical practice
Dynamics over time	Static, single time-point risk assessment	Develop dynamic models with time-updated variables to reflect evolving clinical profiles
Bleeding outcome definition	ISTH bleeding criteria encompass a wide range of bleeding types that differ in predictors and clinical consequences	Consider bleeding type-specific risk scores (e.g., predicting intracranial bleeding)
Lack of patient centered outcomes	Bleeding outcomes are defined solely by clinical criteria, without considering patient perspectives or impact on quality of life	Integrate patient-reported outcome measures (PROMs), and develop patient-reported relevant bleeding outcome

necessary, to further explore the clinical utility of this risk score. This would allow for full validation, including calibration, and potential improvement of predictive performance.

Ultimately, a more refined approach to bleeding risk assessment is needed; one that considers thromboembolic and bleeding risks jointly. Such stratification could guide decisions on full-dose OAC, dose reduction, or refraining from anticoagulation in selected patients. Biomarkers may enhance such stratification, as illustrated by the ABC-AF stroke and bleeding scores, which incorporate, among others, growth-differentiation factor 15 (GDF-15), and outperformed traditional scores (e.g., HAS-BLED and CHA_2DS_2-VASc) [30,31]. The ongoing L-TRIP study in patients with VTE is currently exploring a combined risk score that integrates both thrombosis and bleeding risk, including biomarkers, to guide long-term anticoagulant therapy decisions [32]. Although results are pending, this approach holds promise for adaptation in AF populations and could be investigated in future prospective studies.

Moreover, as the AF population is aging, frailty becomes a key concern. The FRAIL-AF study indicated that switching from VKAs to DOACs in frail elderly patients may increase clinically relevant bleeding without clear efficacy benefits, highlighting the need for careful therapeutic decisions in this subgroup [33]. The Dutch-GERAF study aims to further investigate the efficacy and safety of OACs in frail older AF patients, while also externally validating bleeding risk scores such as the ABC-AF bleeding score [34].

Another important consideration is the heterogeneity of bleeding events. Current definitions of clinically relevant bleeding according to the ISTH criteria encompass a wide range of bleeding types with distinct clinical implications and predictors. This heterogeneity complicates accurate risk prediction. Future research could aim to develop bleeding type-specific risk scores to enhance predictive precision. Furthermore, patient-centered outcomes deserve greater emphasis. Traditional bleeding and thromboembolic endpoints rely on objective clinical definitions that may not capture patient's experience or impact on quality of life. Incorporating patient-reported outcome measures (PROMs) and developing "patient-reported relevant bleeding" risk scores could enhance relevance.

Finally, most bleeding risk scores are static, assessing risk at a single time point and assuming stability over time. In contrast, clinical profiles are dynamic, with key risk factors changing during follow-up. Dynamic prediction models with time-updated variables could offer more accurate and clinically relevant risk estimates by capturing these changes [35]. Such models could support more individualized and proactive management.

4.4. Strengths and limitations

A key strength is the validation of AF-BLEED within a large, nationwide, daily clinical practice cohort, enrolling AF patients from primary care, thrombosis services, and hospitals. Most patients were prospectively followed for two years according to protocol, with data systematically collected through structured telephone interviews and thorough medical records review. Additionally, we evaluated clinically relevant endpoints, including MB and the composite outcome of CRNMB and MB, using predefined and widely accepted ISTH definitions. Moreover, to ensure AF-BLEED was validated as originally intended, predictor definitions where aligned wherever possible, and validation was performed at the intended timeframes (i.e., 180 days and 2 years). At last, we conducted rigorous statistical analyses, accounting for mortality and OAC discontinuation as competing events.

Several limitations merit consideration. Firstly, the absence of model estimates and predicted probabilities in the original AF-BLEED publication precluded formal validation, including calibration assessment. Secondly, despite our large sample size, the low number of high-risk patients and bleeding events may have limited power to detect risk differences between AF-BLEED strata. Lastly, 13 % of patients were excluded due to missing predictor data, under the assumption of MCAR, which may have introduced bias.

5. Conclusions

The cumulative incidence of clinically relevant bleeding in this cohort of newly diagnosed AF patients in daily practice who initiated OAC was higher among patients classified as high-risk by the AF-BLEED score, yet the overall predictive performance of the risk score was limited. There is a lack of guidance for bleeding risk prediction in patients with AF and implications for anticoagulant management. Future studies should address this critical knowledge gap to enhance patient-tailored anticoagulant care and mitigate bleeding risk.

CRediT authorship contribution statement

S.F.B. van der Horst: Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **G. Chu:** Writing – review & editing, Validation, Resources, Project administration, Methodology, Investigation, Conceptualization. **J. Seelig:** Writing – review & editing, Supervision, Resources, Project administration, Investigation. **E.M. Trinks-Roerdink:** Writing – review & editing, Validation, Resources, Project administration, Investigation. **L. Voorhout:** Writing – review & editing, Validation, Project administration, Investigation. **T.A.C. de Vries:** Writing – review & editing, Validation, Resources, Project administration, Investigation. **A.P. van Alem:** Writing – review & editing, Resources, Investigation. **R.J. Beukema:** Writing – review & editing, Resources, Investigation. **L.V.A. Boersma:** Writing – review & editing, Resources, Investigation. **M.A. Brouwer:** Writing – review & editing, Resources, Methodology. **H. ten Cate:** Writing – review & editing, Resources, Investigation. **L.M. Faber:** Writing – review &

editing, Resources, Investigation. **J.R. de Groot:** Writing – review & editing, Resources, Investigation. **Y.L. Gu:** Writing – review & editing, Resources, Investigation. **F.R. den Hartog:** Writing – review & editing, Resources, Investigation. **J.S.S.G. de Jong:** Writing – review & editing, Resources, Investigation. **Y. de Jong:** Writing – review & editing, Resources, Investigation. **C.J.H.J. Kirchhof:** Writing – review & editing, Resources, Investigation. **F.S. Kleijwegt:** Writing – review & editing, Resources, Investigation. **F.A. Klok:** Writing – review & editing, Resources, Investigation. **M.J.H.A. Kruip:** Writing – review & editing, Resources, Investigation. **T. Lenderink:** Writing – review & editing, Resources, Investigation. **J.G. Luermans:** Writing – review & editing, Resources, Investigation. **J.G. Meeder:** Writing – review & editing, Resources, Investigation. **A.M. Otten:** Writing – review & editing, Resources, Investigation. **R. Pisters:** Writing – review & editing, Resources, Investigation. **L. Pos:** Writing – review & editing, Resources, Investigation. **F.J. Prins:** Writing – review & editing, Resources, Investigation. **T.J. Römer:** Writing – review & editing, Resources, Investigation. **F. Smeets:** Writing – review & editing, Resources, Investigation. **G.J.M. Tahapary:** Writing – review & editing, Resources, Investigation. **L.J.H.J. Theunissen:** Writing – review & editing, Resources, Investigation. **R.G. Tieleman:** Writing – review & editing, Resources, Investigation. **S.A.J. Timmer:** Writing – review & editing, Resources, Investigation. **V. Tichelaar:** Writing – review & editing, Resources, Investigation. **S.A. Trines:** Writing – review & editing, Resources, Investigation. **P. van der Voort:** Writing – review & editing, Resources, Investigation. **S. Velthuis:** Writing – review & editing, Resources, Investigation. **E.A. de Vrey:** Writing – review & editing, Resources, Investigation. **R.J. Walhout:** Writing – review & editing, Resources, Investigation. **M.E.W. Hemels:** Writing – review & editing, Supervision, Resources, Project administration, Investigation, Funding acquisition, Conceptualization. **F.H. Rutten:** Writing – review & editing, Resources, Methodology, Investigation. **G.J. Geersing:** Writing – review & editing, Resources, Methodology, Investigation. **M.V. Huisman:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

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During the preparation of this work the authors used ChatGPT in order to partially refine and enhance the written text. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2025.109533.

Data availability

The data underlying this article cannot be shared publicly due to the privacy of individuals that participated in the study.

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