SUPPLEMENTAL MATERIAL

Development and Validation of a Novel Bleeding Risk Prediction Tool for Patients with Atrial Fibrillation

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Supplemental Figures

Supplemental Tables

Supplemental Methods

Supplemental Figure 1. Calibration Plot for Major Bleeding

Presented is the calibration of the continuous model (Figure 1A) and the clinical risk prediction score (Figure 1B) in the RE-LY trial at 1-year. X-axis demonstrates the predicted 1-year event rate without a major bleeding event. The Y-axis demonstrates the actual 1-year major bleeding event rate. The black lines represents perfect calibration, whereas the blue line demonstrates the observed optimism corrected calibration. Optimism correction was done by bootstrapping 200 resamples. Individuals were included if they were in the dabigatran 150 mg arm twice daily of the trial. Individuals with missing information for the candidate variables of interest were excluded.

Figure 1A. Calibration Plot for the Continuous Model

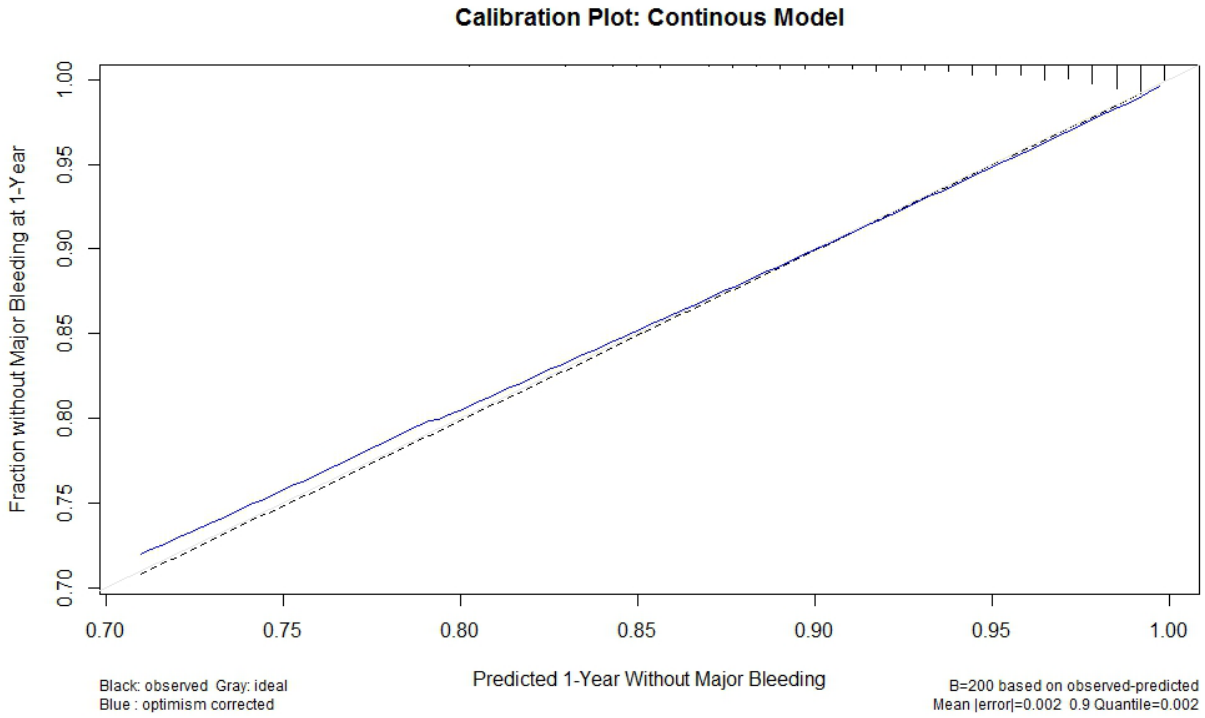
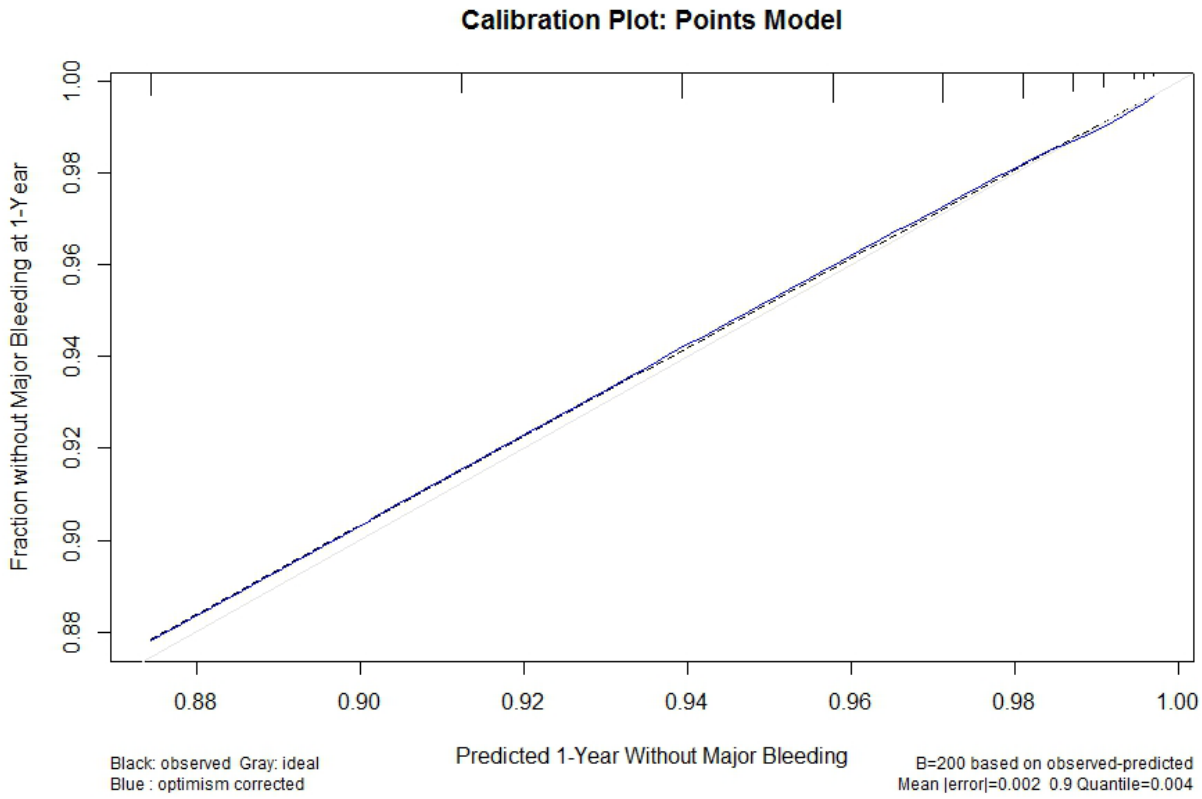
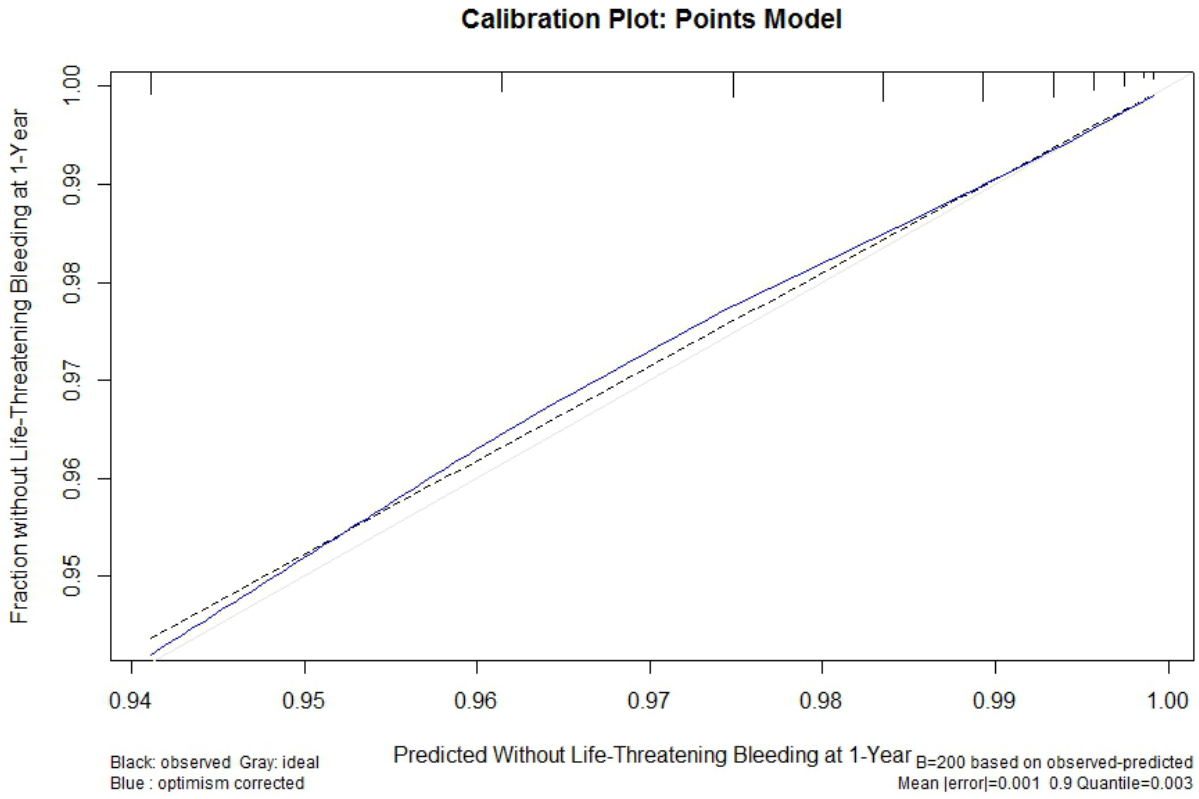


Figure 1B. Calibration Plot for the DOAC Score



Supplemental Figure 2. Calibration Plot, Life-Threatening Bleeding

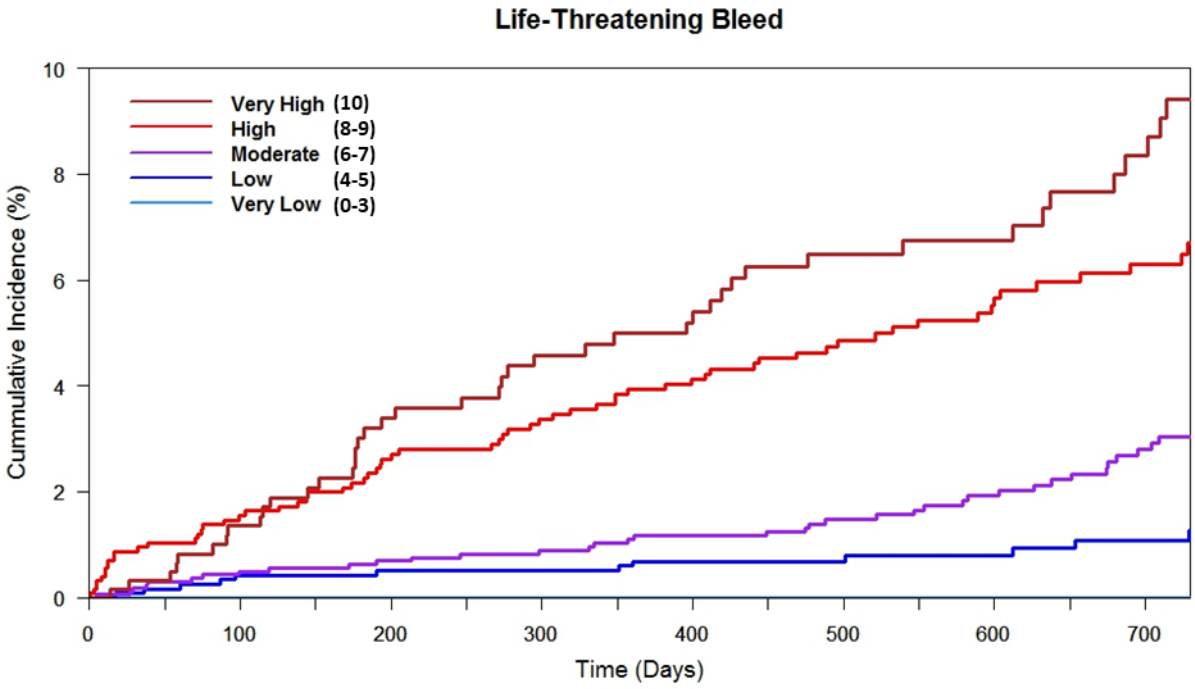
Presented is the calibration of the DOAC Score in the RE-LY trial at 1-year. X-axis demonstrates the predicted 1-year event rate without a life-threatening bleeding event. The Y-axis demosntrates the actual 1-year life-threatening bleeding event rate. The black lines represents perfect calibration, whereas the blue line demonstrates the observed optimism corrected calibration. Optimism correction ws done by bootstrapping 200 resamples. Individuals were included if they were in the dabigatran 150 mg twice daily arm of the trial. Individuals with missing information for the candidate variables of interest were excluded.



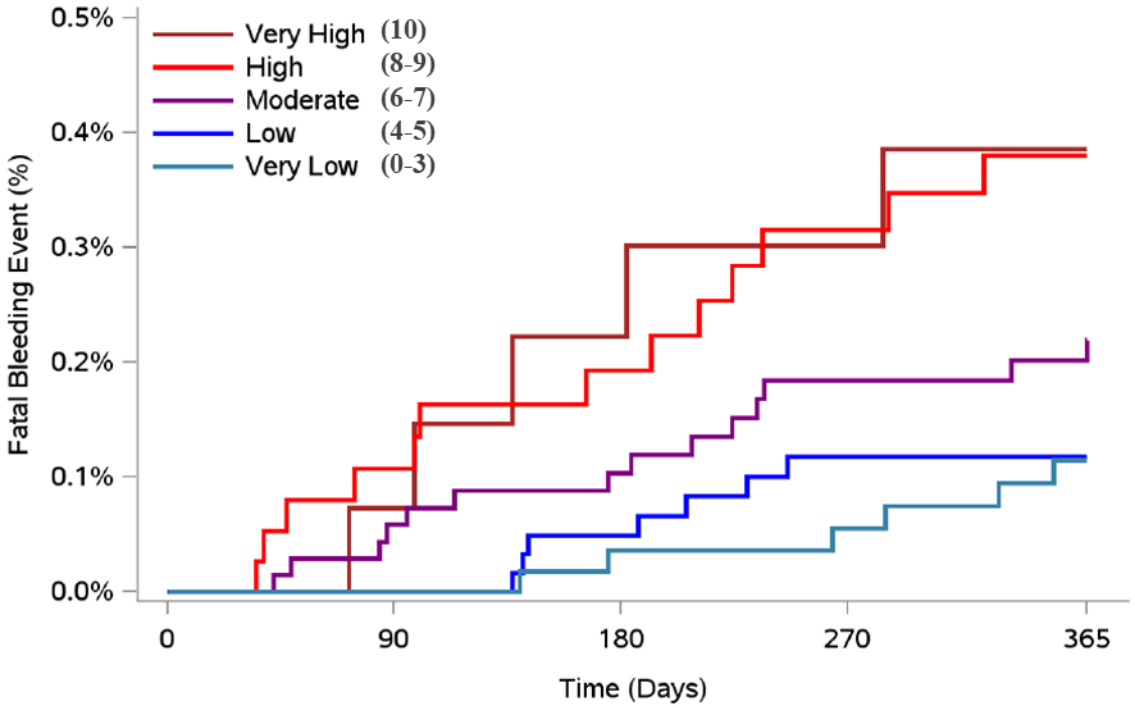
Supplemental Figure 3. Kaplan-Meier Curves for Life-Threatening or Fatal Bleeding Outcomes by Predicted Risk Category

Presented are the Kaplan-Meier curves for individuals in the RE-LY (1A) and COMBINE-AF (1B). The outcome in RE-LY was life-threatening bleeding. The outcome for COMBINE-AF was fatal bleeding. Definitions are described the Supplemental Methods section. Kaplan-Meier curves were based on the risk category assigned to individuals by the DOAC Score. Risk-scores were 1-10, with risk categories assigned as: very low (score 0-3), low (score 4-5), moderate (score 6-7), high (score 8-9) and very high (score 10). Individuals in RE-LY were included if they were in the dabigatran 150 mg twice daily arm of the trial. Individuals in COMBINE-AF were included if they were on any direct-acting oral anticoagulant (DOAC).

A) Kaplan-Meier Curves for Life-Threatening Bleeding by Risk Category in RE-LY

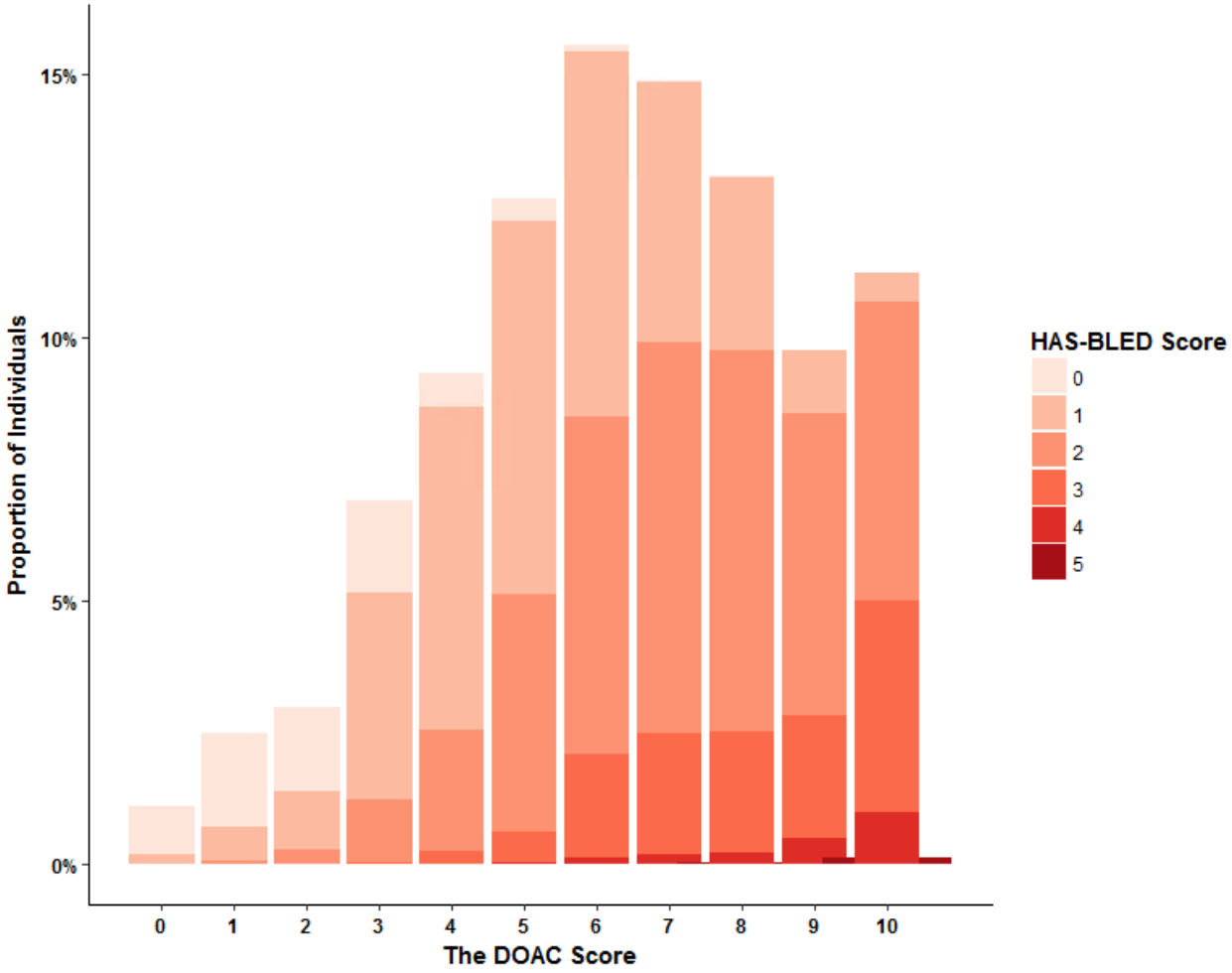


B) Kaplan-Meier Curves for Fatal Bleeding by Risk Category in COMBINE-AF


0.5%
0.4%
0.3%
0.2%
0.1%
0.0%
Fatal Bleeding Event (%)
Very High (10)
High (8-9)
Moderate (6-7)
Low (4-5)
Very Low (0-3)
0
90
180
270
365
Time (Days)

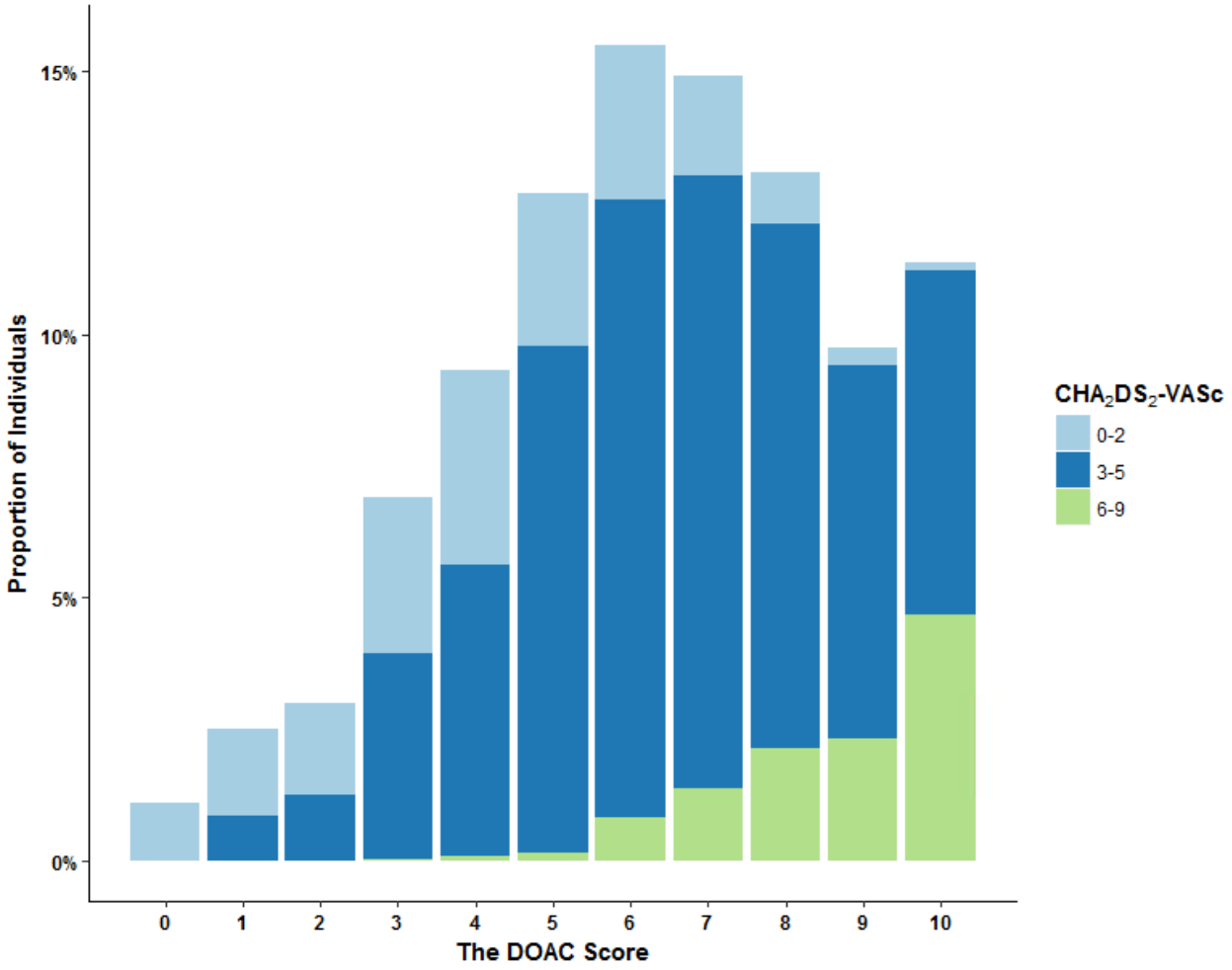
Supplemental Figure 4. The DOAC Score by HAS-BLED Score

Presented are the risk scores assigned by the DOAC Score for individuals in the development cohort (RE-LY) by HAS-BLED score. The X-axis demonstrates the DOAC Score, while the Y axis displays the proportion of individuals with that score. Shading indicates HAS-BLED score. Individuals were included if they were in the dabigatran 150 mg twice daily arm of the trial. Individuals were excluded if they had missing information for the predictor variables of interest or missing data for calculation of the HAS-BLED score. Individuals were followed through their entire enrollment in the trial.



Supplemental Figure 5. The DOAC Score by CHA_2DS_2-VASc Scores

Presented are the risk scores assigned by the DOAC Score for individuals in the development cohort (RE-LY) by CHA_2DS_2-VASc score (Figure 2B). The X-axis demonstrates the DOAC Score, while the Y axis displays the proportion of individuals with that score. Shading indicates CHA_2DS_2-VASc score. Individuals were included if they were in the dabigatran 150 mg twice daily arm of the trial. Individuals were excluded if they had missing information for the predictor variables of interest or missing data for calculation of the CHA_2DS_2-VASc score. Individuals were followed through their entire enrollment in the trial.



Supplemental Table 1. Candidate Variables

Presented are the candidate variables that were considered during model development in the RE-LY trial. Candidate variables were selected based on prior evidence for association with bleeding risk or clinical rationale for ability to predict bleeding events. Smoking history was defined as an individual with smoking history of ≥100 cigarettes over a lifetime. Alcohol use disorder was defined as ≥5 alcohol drinks per week. Body mass index was initially categorized as ≥30 kg/m^2 vs <30 kg/m^2, but was reclassified during recalibration as <18.5 kg/m^2 vs ≥18.5 kg/m^2). Smoking history was excluded on recalibration (see methods section). Creatinine clearance was determined based on the Cockcroft-Gault equation. Due to low inclusion of individuals with bleeding history or liver disease in RE-LY, points for these variables were assigned based on clinical rationale. Clinical rationale incorporated expert perceived risk of clinically significant bleeding history and liver disease for the outcomes of interest. eGFR = estimated glomerular filtration rate.

Candidate Variables	
Age (Years)	
	65-69
	70-74
	75-79
	80-84
	≥85
Sex (Male/Female)	
Body Mass Index (<18.5 kg/m^2 vs ≥18.5 kg/m^2)	
Creatinine Clearance/eGFR (mL/min)	
	30-60
	<30
Smoking History (Prior or Current)	
Alcohol Use Disorder (Alcohol Use ≥5 days per week)	
Stroke, Transient Ischemic Attack, Systemic Embolism History	
Diabetes (History)	
Hypertension (History)	
Coronary Artery Disease (History)	
Antiplatelet Use (Current)	
	Aspirin
	Dual Antiplatelet
Nonsteroidal Anti-Inflammatory Use (Current)	
Heart Failure (History)	
Bleeding History (History of Major or Minor Bleeding Event)	
Liver Disease (AST, ALT, ALP ≥3X Upper limit of normal or ALP ≥2X Upper limit of normal	

Supplemental Table 2. The DOAC Score Prior to Model Refinement

Presented is the original risk score developed prior to the model refinement step outlined in the methods section. In model refinement, weight was converted to underweight/normal weight based and smoking history was removed due to low predictive ability. The prediction model was then refit, allowing for new coefficients (Supplemental Table 3). The prediction score was developed in the RE-LY trial participants, including individuals on direct-acting oral anticoagulants (DOACs). The maximum number of allocated points for an individual is 10 points to prevent overestimation in the high-risk groups.

2A) The DOAC Score Prior to Model Updating

Clinical Risk Prediction Tool	Points
Age, years	
65-69	**2**
70-74	**3**
≥75	**4**
Creatinine Clearance/eGFR (mL/min)	
30-60	**1**
<30	**2**
Obesity (BMI ≥30)	**1**
Smoking History	**1**
Stroke/TIA/Embolism History	**1**
Diabetes	**1**
Hypertension	**1**
Antiplatelet Use	
Aspirin	**2**
Dual-Antiplatelet	**3**
Nonsteroidal Anti-inflammatory (NSAID) Use	**1**

Bleeding History **Liver Disease**	**3** **2**
Total Score Range: 0-10 *(Maximum 10 points)*	

2B) The DOAC Score Performance Prior to Model Refinement

	C Statistic		
	DOAC Score	**HAS-BLED Score**	**P for Difference**
Major Bleeding - RE-LY	0.73 (0.71-0.75)	0.60 (0.58-0.62)	<0.001
Life Threatening Bleeding - RE-LY	0.75 (0.72-0.78)	0.61 (1.29-1.97)	<0.001
Major Bleeding GARFIELD-AF	0.69 (95% CI: 0.65-0.73)	0.66 (0.62-0.71)	0.133

Supplemental Table 3. Final Multivariable Model

Presented are the final variables in the multivariable Cox regression model. The model was developed in the RE-LY trial, among individuals in the dabigatran 150mg twice daily arm of the trial and who had no missing follow-up information. Variables were selected based on a stepwise selection approach. Due to low sample size of individuals with bleeding history and liver disease in the development cohort, these variables were required to be included. Points were assigned to the final clinical risk prediction score by the final coefficients (hazard ratios) for all variables except bleeding history and liver disease. These variables were manually assigned based on clinical rationale due to high likelihood of low event count bias. No variable was allowed more than half of the maximum number of points (5 points). Reference value for point assignment was 1.35 (the value that each hazard ratio was divided by).

Individual Characteristic		**Hazard Ratio**	**P-Value**
Age (Years) (< 65 reference)			
	65-69	2.45	0.001
	70-74	3.48	<0.001
	75-79	4.85	<0.001
	80-84	6.85	<0.001
	≥85	9.82	<0.001
Underweight (BMI <18.5 kg/m^2)		2.00	0.069
Creatinine Clearance (mL/min) (>60 reference)			
	30-60	1.18	0.159
	<30	2.92	0.010
Stroke, Transient Ischemic Attack, or Systemic Embolism History		1.27	0.041
Diabetes		1.53	<0.001
Antiplatelet Use			
	Aspirin	2.67	<0.001
	Dual Antiplatelet	3.77	<0.001
Nonsteroidal Anti-Inflammatory Use		1.36	0.022
Bleeding History		1.08	0.70
Liver Disease		0.49	0.32
Hypertension		1.35	0.033

Supplemental Table 4. Bleeding Event Rates in the RE-LY Trial by Risk Score

Presented are the observed 1-year and 2-year rates of bleeding in the RE-LY trial by the DOAC Score assigned risk scores. Individuals were included if they were in the dabigatran 150 mg twice daily arm of the trial. Individuals with missing information for the candidate variables of interest were excluded. Estimates are based on Cox regression models with clinical risk prediction score as the independent variable.

Risk Score by DOAC Score	Major Bleeding (1-Year)	Life-Threatening Bleeding (1-Year)	Major Bleeding (2-Year)	Life-Threatening Bleeding (2-Year)
0	0.3%	0.1%	0.6%	0.2%
1	0.4%	0.1%	0.8%	0.3%
2	0.6%	0.2%	1.2%	0.4%
3	0.8%	0.3%	1.7%	0.6%
4	1.2%	0.4%	2.4%	1.0%
5	1.8%	0.7%	3.4%	1.4%
6	2.7%	1.0%	4.9%	2.2%
7	4.0%	1.6%	7.0%	3.3%
8	5.8%	2.4%	10.0%	5.0%
9	8.5%	3.7%	14.1%	7.5%
10	12.4%	5.8%	19.7%	11.2%

Supplemental Table 5. Life-Threatening Bleeding Event Rates in the RE-LY Trial by Risk Group

Presented are the observed rates of life-threatening bleeding at 1- year in the RE-LY trial by clinical risk group. Risk category was assigned by the clinical risk prediction score based on 1-year projected rate of major bleeding. Individuals were included if they were included in the dabigatran 150 mg arm of the trial. Individuals with missing information for the candidate variables of interest were excluded. Estimates are based on Cox regression models with risk group as the independent variable.

Risk Group	Risk Score by DOAC Score	N	Major Bleeding (1-Year)	Life-Threatening Bleeding (1- Year)
Very Low	0-3	767	0.8%	0.3%
Low	4-5	1249	1.6%	0.6%
Moderate	6-7	1727	3.4%	1.4%
High	8-9	1296	6.9%	2.9%
Very High	10	645	13.9%	6.3%

Supplemental Table 6. Cohort Variables and Adaptations: GARFIELD-AF

Presented are the variables used in the development cohort (RE-LY trial) and the definitions of the similar variables in the refinement cohort (GARFIELD-AF). CKD = Chronic kidney disease. ASA = Aspirin. DAPT = Dual antiplatelet therapy. NSAID = Nonsteroidal anti-inflammatory drug.

Risk score variables and categories	POINTS	GARFIELD-AF ADAPTATIONS
• Age		
○ 65-69	2	*Same*
○ 70-74	3	
○ 75-79	4	
○ 80-84	5	
○ ≥85	5	
• Creatinine Clearance/eGFR		*CKD stage*
○ 30-60	1	*Stage III*
○ <30	2	*Stage IV or V*
• Underweight (BMI ≤18.5)	1	*Same*
• Stroke/TIA/Embolism history	1	*Same*
• Diabetes	1	*Same*
• Hypertension	1	*Same*[1]
• Antiplatelet use		
○ ASA	2	*Same*
○ DAPT	3	
• NSAID use	1	*Same*[2]
• Bleeding history	3	*Same*
• Liver disease	2	Cirrhosis

[1]Defined as CRF-reported hypertension or systolic blood pressure >140 or diastolic blood pressure >90;
[2]NSAID use including individuals on Cox inhibitors

Supplemental Table 7. Cohort Variables and Adaptations: COMBINE-AF

Presented are the variables used in the development cohort (RE-LY trial) and the definitions of the similar variables in the validation cohort (COMBINE-AF). CKD = Chronic kidney disease. ASA = Aspirin. DAPT = Dual antiplatelet therapy. NSAID = Nonsteroidal anti-inflammatory drug.

Risk score variables and categories	POINTS	COMBINE-AF ADAPTATIONS
• Age		
○ 65-69	2	*Same*
○ 70-74	3	
○ 75-79	4	
○ 80-84	5	
○ ≥85	5	
• Creatinine Clearance/eGFR		*Same*
○ 30-60	1	
○ <30	2	
• Underweight (BMI ≤18.5)	1	*Same*
• Stroke/TIA/Embolism history	1	*Same*
• Diabetes	1	*Same*
• Hypertension	1	*Same*[1]
• Antiplatelet use		
○ ASA	2	*Same*
○ DAPT	3	
• NSAID use	1	*Same*
• Bleeding history	3	*Same*
• Liver disease	2	*Same*

Supplemental Table 8. Cohort Variables and Adaptations: RAMQ

Presented are the variables used in the development cohort (RE-LY trial) and the definitions of the similar variables in the validation cohort (RAMQ) (A). Also presented are the ICD-9 and ICD-10 codes used for definitions (B). CKD = Chronic kidney disease. ASA = Aspirin. DAPT = Dual antiplatelet therapy. NSAID = Nonsteroidal anti-inflammatory.

A) RAMQ Variable Adaptations – Overview

Risk score variables and categories	POINTS	GARFIELD-AF ADAPTATIONS
• Age		
○ 65-69	2	*Same*
○ 70-74	3	
○ 75-79	4	
○ 80-84	5	
○ ≥85	5	
• Creatinine Clearance/eGFR		*CKD stage*
○ 30-60	1	*Stage III*
○ <30	2	*Stage IV or V*
• Underweight (BMI ≤18.5)	1	*ICD9/10 Codes*
• Stroke/TIA/Embolism history	1	*ICD9/10 Codes*
• Diabetes	1	*ICD9/10 Codes*
• Hypertension	1	*ICD9/10 Codes*
• Antiplatelet use		
○ ASA	2	*Dispensation of ASA within the 2 weeks preceding the DOAC initiation*
○ DAPT	3	*Combination of two antiplatelet dispensations within the 2 weeks preceding the DOAC initiation*
• NSAID use	1	*Dispensation of NSAID within the 2 weeks*

		preceding the DOAC initiation
• Bleeding history	3	*ICD9/10 Codes*
• Liver disease	2	*ICD9/10 Codes*

B) RAMQ Variable Adaptations: ICD-9 & ICD-10 Codes

	ICD-9 codes	**ICD-10 codes**
Underweight	783.2, 783.22	R63.6, V85.0
Stroke/TIA/Embolism history	362.31, 362.32, 433.xx, 434.xx, 435.x, 436,444.x, 557.0, 598.31	G45, H34.1, H34.2, I63 except 63.6, I67.89, I74, K55.0, N28.0
Diabetes	250.xx, 357.2x, 362.0x, 366.41	E10.xx, E11.xx, E12.xx, E13.xx, E14.xx
Hypertension	401.xx	I10.xx
Bleeding History	430, 431, 432.x, 456.1, 530.7, 531.0x, 531.2x, 531.4x, 531.6x, 532.0x, 532.2x, 532.4x. 532.6x, 533.0x. 533.2x, 533.4x, 533.6x, 534.0x, 534.2x, 534.4x, 534.6x, 535.1, 537.83, 562.02, 562.03, 562.12, 562.13, 569.3x, 569.85, 578.0 578.1x, 578.9, 852.x, 853.x	I60, I61, I62, I85.0, K22.6, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K31.811, K57.11, K57.13, K57.31, K57.33, K62.5, K55.21, K92.0, K92.1, K92.2, S06.3, S06.4, S06.5, S06.6
Liver Disease	570.xx, 571.xx	K70.xx – K74.xx

Supplemental Table 9. Baseline Characteristics by Major Bleeding Occurrence in GARFIELD-AF

Presented are baseline characteristics of individuals in the GARFIELD-AF cohort by occurrence of major bleeding. Individuals were included if they were treated with a direct-acting oral anticoagulant and had no missing follow-up information.

Baseline characteristics	Major bleeding occurrence	
	No (N=12,105)	Yes (N=191)
Sex, n (%)		
Male	6799 (56.2)	98 (51.3)
Female	5306 (43.8)	93 (48.7)
Age, median (Q1; Q3), years	72.0 (64.0;79.0)	78.0 (71.0;82.0)
Age, n (%), years		
<65	3118 (25.8)	20 (10.5)
65-69	1982 (16.4)	23 (12.0)
70-74	2220 (18.3)	29 (15.2)
≥75	4785 (39.5)	119 (62.3)
Ethnicity, n (%)		
Caucasian	7670 (65.0)	133 (73.1)
Hispanic/Latino	519 (4.4)	4 (2.2)
Asian	3325 (28.2)	40 (22.0)
Afro-Caribbean/Mixed/Other	284 (2.4)	5 (2.7)
Body Mass Index (BMI), median (Q1;Q3), kg/m^2	26.8 (23.8;30.7)	26.0 (23.0;29.8)
BMI, n (%), kg/m^2		
<18.5	172 (1.8)	11 (7.1)
18.5-24.9	3225 (33.4)	55 (35.7)
25.0-29.9	3504 (36.3)	50 (32.5)
≥30.0	2762 (28.6)	38 (24.7)
Systolic blood pressure, median (Q1; Q3), mmHg	132.0 (120.0;145.0)	135.0 (121.0;145.0)
Diastolic blood pressure, median (Q1; Q3), mmHg	80.0 (70.0;88.0)	80.0 (70.0;87.0)
Pulse, median (Q1; Q3), bpm	85.0 (70.0;107.0)	82.0 (70.0;112.0)
Type of atrial fibrillation, n (%)		
Permanent	1411 (11.7)	19 (9.9)
Persistent	2042 (16.9)	26 (13.6)
Paroxysmal	3962 (32.7)	54 (28.3)
New onset (unclassified)	4690 (38.7)	92 (48.2)
Care setting specialty at diagnosis, n (%)		
Internal medicine/Neurology/Geriatrics	2128 (17.6)	43 (22.5)

Cardiology	8673 (71.6)	127 (66.5)
Primary care/General practice	1304 (10.8)	21 (11.0)
Care setting location at diagnosis, n (%)		
Hospital	5919 (48.9)	108 (56.5)
Office/Anticoagulation clinic/thrombosis centre	5070 (41.9)	64 (33.5)
Emergency room	1116 (9.2)	19 (9.9)
Medical history, n (%)		
Heart failure	2538 (21.0)	42 (22.0)
Acute coronary syndromes	1138 (9.4)	21 (11.0)
Vascular disease[1]	2563 (21.4)	46 (24.1)
Carotid occlusive disease	376 (3.2)	12 (6.4)
VTE	284 (2.4)	9 (4.7)
Prior stroke/TIA/SE	1299 (10.8)	31 (16.4)
Prior bleeding	226 (1.9)	6 (3.2)
Hypertension	9212 (76.3)	154 (81.1)
Hypercholesterolaemia	5147 (44.0)	81 (43.3)
Diabetes	2587 (21.4)	52 (27.2)
Cirrhosis	37 (0.3)	4 (2.1)
Dementia	200 (1.7)	5 (2.7)
CKD stage, n (%)		
None, Stage I or II (GFR ≥60)	10540 (90.2)	148 (79.6)
Stage III (GFR 30-59)	1079 (9.2)	33 (17.7)
Stage IV or V (GFR <30)	67 (0.6)	5 (2.7)
Heavy alcohol consumption, n (%)	200 (2.0)	5 (3.3)
Current smoker, n (%)	3914 (35.6)	57 (32.4)
ASA therapy	1273 (10.5)	26 (13.6)
DAP therapy	310 (2.6)	9 (4.7)
NSAID therapy	449 (3.7)	18 (9.4)
CHA_2DS_2-VASc score, median (Q1; Q3)	3.0 (2.0;4.0)	4.0 (3.0;5.0)
HAS-BLED score, median (Q1; Q3)[2]	1.0 (1.0;2.0)	2.0 (1.0;2.0)
GARFIELD death score, median (Q1; Q3)[3]	3.8 (2.2;6.9)	6.5 (3.8;9.9)
GARFIELD stroke score, median (Q1; Q3)[4]	1.2 (0.9;1.8)	1.7 (1.2;2.3)
GARFIELD bleeding score, median (Q1; Q3)[5]	1.4 (1.0;2.1)	1.9 (1.5;2.8)

[1]Defined as peripheral artery disease and/or coronary artery disease;

[2]The risk factor 'Labile INRs' is not included in the HAS-BLED score as it is not collected at baseline. As a result, the maximum HAS-BLED score at baseline is 8 points (not 9);

[3]Represent the risk of mortality within 2 years;

[4]Represent the risk of non-haemorrhagic stroke within 2 years;

[5]Represent the risk of major bleeding within 2 years.

Supplemental Table 10. Baseline Characteristics by Major Bleeding Occurrence in COMBINE-AF

Presented are baseline characteristics of individuals in the COMBINE-AF cohort by occurrence of major bleeding. Individuals were included if they were treated with a direct-acting oral anticoagulant.

Major Bleeding Outcome	No (N=24,894)	Yes (N=692)
Age		
<65	6825 (27.4)	113 (16.3)
65-69	4014 (16.1)	102 (14.7)
70-74	4903 (19.7)	107 (15.5)
75-79	5232 (21)	189 (27.3)
>=80	3920 (15.7)	181 (26.2)
Creatinine Clearance		
>60	16,514 (66.3)	374 (54)
30-60	8131 (32.7)	310 (44.8)
<30	249 (1)	8 (1.2)
Body Mass Index < 18.5	264 (1.1)	11 (1.6)
Stroke/TIA/Embolism history	7507 (30.2)	254 (36.7)
Diabetes	7828 (31.4)	272 (39.3)
Hypertension	22,328 (89.7)	621 (89.7)
Antiplatelet use		
Aspirin	7845 (31.5)	297 (42.9)
Dual Antiplatelet	445 (1.8)	24 (3.5)
NSAID use	1055 (4.2)	46 (6.6)
Bleeding history	2310 (9.3)	106 (15.3)
Liver disease	109 (0.4)	3 (0.4)
Age - Mean(SD)	70 (9.5)	73.5 (8.6)
Female	9436 (37.9)	222 (32.1)
Race		
White	20,394 (81.9)	570 (82.4)
Black	305 (1.2)	12 (1.7)
Asian	3536 (14.2)	95 (13.7)
Other	659 (2.6)	15 (2.2)
CHA_2DS_2-VASc– Mean (SD)	4 (1.6)	4.6 (1.4)
HAS-BLED – Mean (SD)	2.4 (1.1)	2.8 (1.1)
Smoking history (current or former)	10,270 (41.3)	345 (49.9)

Supplemental Table 11. Baseline Characteristics by Major Bleeding Occurrence in RAMQ

Presented are baseline characteristics of individuals in the RAMQ cohort by occurrence of major bleeding. Individuals were included if they were treated with rivaroxaban (20mg daily) or apixaban (5mg twice per day). The cohort included adults hospitalized between 2011 and 2017.

Baseline Characteristics	**Major bleeding occurrence**	
	Yes (n=258)	**No** (n=11,687)
Age – mean (SD)	78.4 (7.6)	75.1 (8.9)
Male - %	52.7%	52.9%
CHA_2DS_2-VASc Score – mean (SD)	3.7 (1.3)	3.2 (1.4)
HAS-BLED Score – mean (SD)	3.1 (1.2)	2.8 (1.3)
Charlson Score Index – mean (SD)	4.8 (3.5)	4.0 (3.4)
Comorbidities - %		
Hypertension	83.7 %	77.2 %
Dyslipidemia	57.0%	52.4%
Diabetes	41.9%	33.9%
Coronary artery disease	55.4%	44.5%
Acute myocardial infarction	13.2%	10.0%
Chronic heart failure	38.9%	29.4%
Cardiomyopathy	10.5%	6.5%
Other dysrhythmias	17.8%	18.5%
Valvular disease	20.2%	14.2%
Prior cerebrovascular disease including TIA	17.4%	16.5%
Peripheral vascular disease	26.4%	17.4%
Chronic renal failure	28.3%	23.0%
Chronic renal failure < 30 mL/min	4.3%	1.6%
Acute renal failure	20.2%	15.2%
Chronic obstructive pulmonary disease/asthma	43.8%	35.8%
Liver disease	3.1%	2.3%
Depression	12.4%	10.7%
Medical procedures (3 years prior to cohort entry) - %		
Cardiac catheterization	5.0%	3.4%
Percutaneous coronary intervention – Stent	3.1%	2.0%
Coronary artery bypass grafting	0.4%	0.7%
Medications in the 2-week prior to cohort entry - %		
Diuretics	39.5%	30.8%
Loop diuretics	30.6%	23.8%
B-Blockers	57.0%	63.9%
Inhibitors of renin-angiotensin system	33.3%	35.6%
Calcium channel blockers	34.9%	34.2%
Statin	50.0%	43.2%
Antidiabetics	23.3%	20.0%
Low dose ASA	26.7%	20.7%

Proton pump inhibitors	43.8%	40.2%
NSAIDs	1.9%	1.3%
Digoxin	9.3%	8.9%
Health medical service in 3-y prior to cohort entry		
Mean number of specialty visits - mean (SD)	4.2 (6.0)	3.7 (6.0)
Mean number of family physician visits - mean (SD)	3.1 (7.5)	2.6 (5.8)
Mean number of emergency visits - mean (SD)	5.2 (4.7)	4.3 (4.4)
Health hospital service in 3-year prior to cohort entry		
Mean number of all-cause hospital admission - mean (SD)	2.4 (1.9)	2.1 (1.9)
Length of stay - mean (SD)	8.3 (8.4)	7.8 (10.3)

Supplemental Table 12. One-Year Bleeding Rates by Risk Category for Individuals in COBMINE-AF

Presented are the 1-year estimates of intracranial bleeding in COMBINE-AF by the DOAC Score assigned risk category. Risk categories were assigned by the DOAC Score based on risk score. Each individual could be assigned a risk score from 0-10, with the following risk categories: very low (score 1-3), low (score 4-5), moderate (score 6-7), high (score 8-9) and very high (score 10).

Risk Group	Risk Score by DOAC Score	N	Intracranial Bleeding Events	Intracranial Bleeding Rate (1-Year)
Very Low	0-3	6038	19	0.3
Low	4-5	6630	20	0.3
Moderate	6-7	7348	27	0.4
High	8-9	4015	26	0.8
Very High	10	1555	7	0.6

Supplemental Table 13. The DOAC Score Performance by Trial in COBMINE-AF

Presented is the performance of the DOAC Score by trial included in COMBINE-AF for major bleeding (A) and fatal bleeding (B). C-statistics are presented with 95% confidence intervals. The P-value comparing the performance of the DOAC Score and HAS-BLED score in the overall cohort used deLong P-values based on a year risk. The overall comparison involved models adjusted for trial. Number of events are events in one-year.

A) Major Bleeding

Trial	N	Number of Events	DOAC Score, C-Statistic	HAS-BLED score, C-Statistic	P-value
ARISTOTLE	8999	188	0.66 (0.61 - 0.70)	0.61 (0.57 - 0.65)	
ROCKET	7055	253	0.63 (0.60 - 0.67)	0.55 (0.52 - 0.58)	
ENGAGE	6819	213	0.64 (0.60 - 0.68)	0.63 (0.59 - 0.66)	
AVERROES	2713	38	0.71 (0.62 - 0.80)	0.64 (0.55 - 0.73)	
OVERALL	25586	692	0.67 (0.64 - 0.69)	0.63 (0.61 - 0.65)	<0.001

B) Fatal Bleeding

Trial	N	Number of Events	DOAC Score, C-Statistic	HAS-BLED score, C-Statistic	P-value
ARISTOTLE	8999	5	0.72 (0.47 - 0.97)	0.54 (0.30 - 0.78)	
ROCKET	7055	23	0.63 (0.51 - 0.75)	0.55 (0.44 - 0.66)	
ENGAGE	6819	14	0.59 (0.44 - 0.74)	0.55 (0.41 - 0.69)	
AVERROES	2713	3	0.77 (0.44 - 1.10)	0.48 (0.17 - 0.80)	
OVERALL	25586	45	0.72 (0.63 - 0.80)	0.68 (0.60 - 0.77)	0.14

Supplemental Table 14. TRIPOD Checklist: Prediction Model Development and Validation

Section/Topic	Item		Checklist Item	Page
Title and abstract				
Title	1	D; V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	D; V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	2
Introduction				
Background and objectives	3a	D; V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	4-5
	3b	D; V	Specify the objectives, including whether the study describes the development or validation of the model or both.	4-5
Methods				
Source of data	4a	D; V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	5-6, 9-11
	4b	D; V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	5-6, 9-12
Participants	5a	D; V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	5-6, 9-12
	5b	D; V	Describe eligibility criteria for participants.	5-12
	5c	D; V	Give details of treatments received, if relevant.	5-12
Outcome	6a	D; V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	7, 10-12, Supplemental
	6b	D; V	Report any actions to blind assessment of the outcome to be predicted.	NA (Secondary analysis)
Predictors	7a	D; V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	Supplemental
	7b	D; V	Report any actions to blind assessment of predictors for the outcome and other predictors.	NA (Secondary analysis)
Sample size	8	D; V	Explain how the study size was arrived at.	5-6, 9-12

Missing data	9	D; V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	6, 8-9
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	8
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	8-9
	10c	V	For validation, describe how the predictions were calculated.	9-11
	10d	D; V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	5-12
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	8-9, Supplemental
Risk groups	11	D; V	Provide details on how risk groups were created, if done.	8
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	9-12, Supplemental
Results				
Participants	13a	D; V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	12-13,16-17
	13b	D; V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	6, 8-9, Table 1, Supplemental
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	Supplemental
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	Table 3
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	NA
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	Supplemental
	15b	D	Explain how to the use the prediction model.	Table 2
Model performance	16	D; V	Report performance measures (with CIs) for the prediction model.	Table 3
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	Supplemental
Discussion				
Limitations	18	D; V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	19

Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	17
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	17-19
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	17-19
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	12
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	20

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.

Supplemental Methods

Definitions of Major Bleeding

RE-LY: Defined per the International Society on Thrombosis and Haemostasis (ISTH) criteria: a 20 gram per liter reduction in hemoglobin, 2-unit transfusion need, fatal bleeding, or symptomatic bleeding in a critical area or organ.

GARFIELD-AF: Defined per the ISTH criteria: a 20 gram per liter reduction in hemoglobin, 2-unit transfusion need, fatal bleeding, or symptomatic bleeding in a critical area or organ.

COMBINE-AF: Defined per the ISTH criteria: a 20 gram per liter reduction in hemoglobin, 2-unit transfusion need, fatal bleeding, or symptomatic bleeding in a critical area or organ. Any bleeding events occurring intracranial were reported in Supplemental Table 12.

RAMQ Database: Defined by ICD-9 and ICD-10 billing codes as listed below, including billing codes for major intracranial bleeding and major gastroenterological (GI) bleeding. The major intracranial bleeding category was used to provide estimates for intracranial bleeding events (see results).

ICD-9 and ICD-10 Billing Codes Used in RAMQ to define major bleeding:

	ICD-9 codes	ICD-10 codes
Major bleeding		
Major intracranial bleeding	430, 431, 432.x, 852.x, 853.x (primary diagnosis or the first secondary diagnosis using Med-Echo)	I60, I61, I62, S06.3, S06.4, S06.5, S06.6 (primary diagnosis or the first secondary diagnosis using Med-Echo)
Major GI bleeding		
Upper gastrointestinal bleeding (only using Med-Echo)	456.1, 530.7, 531.0x, 531.2x, 531.4x, 531.6x, 532.0x, 532.2x, 532.4x. 532.6x, 533.0x. 533.2x, 533.4x, 533.6x, 534.0x, 534.2x, 534.4x, 534.6x, 535.1, 537.83, 578.0 (primary diagnosis only using Med-Echo)	I85.0, K22.6, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K31.811, K92.0 (primary diagnosis only using Med-Echo)
Upper gastrointestinal bleeding (only using RAMQ)	456.1, 530.7, 531.0x, 531.2x, 531.4x, 531.6x, 532.0x, 532.2x, 532.4x. 532.6x, 533.0x, 533.2x, 533.4x, 533.6x, 534.0x, 534.2x, 534.4x, 534.6x, 535.1, 537.83, 578.0 RAMQ ICD-9 at an emergency room and procedure endoscopic control of	I85.0, K22.6, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K31.811, K92.0 RAMQ ICD-9 at an emergency room and procedure endoscopic control of gastric or duodenal bleeding or

	gastric or duodenal bleeding or upper gastrointestinal endoscopy including esophagus, stomach, and either the duodenum and/or jejunum as appropriate with control of bleeding, any method (code 00691) within 7 days	upper gastrointestinal endoscopy including esophagus, stomach, and either the duodenum and/or jejunum as appropriate with control of bleeding, any method (00691) within 7 days
Lower gastrointestinal bleeding	562.02, 562.03, 562.12, 562.13, 569.3x, 569.85, 578.1x, 578.9 (primary diagnosis only using Med-Echo)	K57.11, K57.13, K57.31, K57.33, K62.5, K55.21, K92.1, K92.2 (primary diagnosis only using Med-Echo)