

[APPENDIX]

Improved risk-stratification of patients with atrial fibrillation: an integrated GARFIELD-AF tool for the prediction of mortality, stroke and bleed in patients with and without anticoagulation

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Supplementary Table 1. Specification for full model

Variable (collected at the time of enrollment)	GARFIELD-AF Definition	ORBIT-AF Definition
Age in years	Age at the time of diagnosis	Age at the time of enrolment into the registry
Pulse	Pulse (bpm)	Pulse (bpm)
Systolic blood pressure	Systolic Blood Pressure (mm Hg)	Systolic Blood Pressure (mm Hg)
Body mass index (kg/m ²)	$weight (kg)/[height (m)]^2$	$weight (kg)/[height (m)]^2$
Vascular disease	Myocardial infarction or unstable angina or peripheral aortic or artery disease	History of coronary artery disease or peripheral vascular disease
Diabetes	Medical history of diabetes	Medical history of diabetes
Cirrhosis	<i>Medical history of cirrhosis</i>	Medical history of alcohol abuse
Peripheral vascular disease	<i>Medical history of peripheral aortic or artery disease</i>	Medical history of peripheral vascular disease
Stroke	<i>Medical history of stroke</i>	Medical history of stroke
Bleed	<i>Medical history of bleeding</i>	Medical history of gastrointestinal bleeding
Heart failure	<i>Medical history of heart failure or an ejection fraction < 40. If ejection fraction is not available, use medical history of heart failure only.</i>	Medical history of heart failure or an ejection fraction of < 40. <i>If ejection fraction is not available, use medical history of heart failure only.</i>
Chronic kidney disease	<i>Chronic kidney disease levels of III-V.</i>	eGFR < 60 with eGFR estimated using the MDRD method.
Sleep Apnoea	<i>Sleep apnoea</i>	Obstructive sleep apnoea
Asia	<i>China, India, Japan, Korea, Thailand, Singapore</i>	0
Other region	<i>Australia, New Zealand, South Africa</i>	0
Race Ethnicity =Black/ Mixed/ Other	<i>(Afro-Caribbean, Mixed race, Other) versus (Caucasian, Hispanic/Latino, Asian)</i>	(Black / African-American, American Indian, Native Hawaiian, Other) versus (Caucasian, Asian)
Paroxysmal atrial fibrillation	<i>Type of atrial fibrillation is paroxysmal at the time of enrolment</i>	Type of atrial fibrillation is paroxysmal at the time of enrolment
Oral anticoagulant use	At enrolment, patient is given or already taking a Vitamin K	At enrolment, patient is given or already taking Warfarin or

	antagonist or <i>Rivaroxaban or Apixaban or Edoxaban or Dabigatran</i>	<i>Rivaroxaban or Apixaban or Edoxaban or Dabigatran</i>
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The following formulas can be used to predict the one year risk of each event:

- All-cause mortality =**
 $1 - [0.986906349 \exp(0.054469698 * (\text{age} - 60) + 0.007435872 * (\text{pulse} - 80) - 0.008242105 * (\text{systolic blood pressure} - 120) - 0.043376577 * (\text{body mass index} - 35) + 0.275702906 * \text{vascular disease} + 0.273433802 * \text{diabetes} + 0.958511573 * \text{cirrhosis} + 0.163472077 * \text{peripheral vascular disease} + 0.329901048 * \text{stroke} + 0.412632047 * \text{bleed} + 0.786437841 * \text{heart failure} + 0.50730543 * \text{chronic kidney disease} + 0.560397093 * \text{sleep apnea} - 0.457744013 * \text{Asia} + 0.41836108 * \text{Other Region} + 0.31701408 * \text{Black, Mixed, Other Race} - 0.368534524 * \text{paroxysmal atrial fibrillation} - 0.443620343 * \text{Oral Anticoagulant})]$
- All-cause mortality reduced model =**
 $1 - [0.984417795 \exp(0.060208102 * (\text{age} - 60) + 0.008235567 * (\text{pulse} - 80) - 0.008211021 * (\text{systolic blood pressure} - 120) + 0.406906988 * \text{vascular disease} + 0.512334926 * \text{bleed} + 0.780055766 * \text{heart failure} + 0.554435057 * \text{chronic kidney} - 0.422166311 * \text{Oral Anticoagulant})]$
- Ischemic stroke or systemic embolism =**
 $1 - [0.991344397 \exp(0.03048226 * (\text{age} - 60) + 0.952524717 * \text{stroke} + 0.432357326 * \text{bleed} + 0.319129628 * \text{heart failure} + 0.574919171 * \text{chronic kidney disease} + 0.654249546 * \text{Other Region} + 0.671380382 * \text{Black/ Mixed/ Other race} - 0.582045773 * \text{Oral Anticoagulant})]$
- Hemorrhagic stroke or major bleed**
 $= 1 - [0.991344397 \exp(0.042943 * (\text{age} - 60) + 0.42205 * \text{vascular disease} + 0.60985 * \text{chronic kidney disease})]$

Supplementary Table 2. Wald Chi-square, p-values and hazard ratios for components of the simplified GARFIELD-AF models

Model	Chi-Square	P-value	Hazard Ratio	95% CI
All-cause mortality				
Age*	492	<.0001	1.35	(1.32, 1.39)
Heart failure	230	<.0001	2.18	(1.97, 2.41)
Pulse*	86	<.0001	1.04	(1.03, 1.05)
OAC use at baseline	69	<.0001	0.66	(0.59, 0.72)
Chronic kidney disease	68	<.0001	1.74	(1.52, 1.99)
Vascular disease	48	<.0001	1.50	(1.34, 1.69)
Systolic blood pressure*	39	<.0001	0.96	(0.95, 0.97)
History of bleeding	24	<.0001	1.67	(1.36, 2.05)
Ischemic stroke or SE				
History of stroke	66	<.0001	2.59	(2.06, 3.26)
Age*	44	<.0001	1.17	(1.11, 1.22)
OAC use at baseline	40	<.0001	0.56	(0.47, 0.67)
Chronic kidney disease	21	<.0001	1.78	(1.39, 2.28)
Australia, New Zealand, South Africa versus other regions	11	0.0007	1.92	(1.32, 2.81)
Heart failure	10	0.0016	1.38	(1.13, 1.68)
Black/ Mixed/ Other races	7	0.0063	1.96	(1.21, 3.17)
History of bleeding	5	0.0314	1.54	(1.04, 2.29)
Major Bleeding (including haemorrhagic stroke)				
Age	55	<.0001	1.23	(1.16, 1.30)
Chronic kidney disease	19	<.0001	1.79	(1.38, 2.32)
Vascular disease	10	0.0017	1.49	(1.16, 1.91)

* Hazard Ratios with 95% confidence intervals (CI) for age, pulse, systolic blood pressure are based on incremental units of '5'. OAC, oral anticoagulant

Supplementary Table 3. Baseline characteristics patients with CHA₂DS₂-VASc 0-2 [men] or 1-3 [women] compared with remaining cohort (CHA₂DS₂-VASc score of ≥ 3 for men and ≥ 4 for women)

	CHA ₂ DS ₂ -VASc 0-2 [men] or 1-3 [women] N=17566	Remaining cohort N=21369	Overall N=38935	P-Value
Age	63.0 (56-70)	77.0 (71-81)	71.0 (63-78)	<.001
Systolic Blood Pressure	130.0 (120-140)	135.0 (120-148)	131.0 (120-145)	<.001
Diastolic Blood Pressure	80.0 (70-89)	80.0 (70-88)	80.0 (70-88)	<.001
BMI	27.0 (24-31)	27.0 (24-31)	27.0 (24-31)	<.001
Pulse	84.0 (70-107)	84.0 (70-103)	84.0 (70-105)	<.001
Type of AF				<.001
Permanent	1788 (10.2%)	3150 (14.7%)	4938 (12.7%)	
Persistent	2707 (15.4%)	3217 (15.1%)	5924 (15.2%)	
Paroxysmal	5394 (30.7%)	5394 (25.2%)	10788 (27.7%)	
New	7677 (43.7%)	9608 (45.0%)	17285 (44.4%)	
Female	6670 (38.0%)	10637 (49.8%)	17307 (44.5%)	<.001
Race				<.001
Caucasian	10142 (57.7%)	14015 (65.6%)	24157 (62.0%)	
Hispanic-Latino	1069 (6.1%)	1547 (7.2%)	2616 (6.7%)	
Afro-Caribbean	64 (0.4%)	54 (0.3%)	118 (0.3%)	
Asian (Not Chinese)	4635 (26.4%)	3909 (18.3%)	8544 (21.9%)	
Chinese	1037 (5.9%)	1029 (4.8%)	2066 (5.3%)	
Mixed/Other	265 (1.5%)	303 (1.4%)	568 (1.5%)	
Unwilling to declare/not recorded	354 (2.0%)	512 (2.4%)	866 (2.2%)	

	CHA ₂ DS ₂ -VASc 0-2 [men] or 1-3 [women] N=17566	Remaining cohort N=21369	Overall N=38935	P-Value
World Region				<.001
Europe	9397 (53.5%)	13105 (61.3%)	22502 (57.8%)	
North America	447 (2.5%)	664 (3.1%)	1111 (2.9%)	
Latin America	1371 (7.8%)	1896 (8.9%)	3267 (8.4%)	
Asia	5838 (33.2%)	5013 (23.5%)	10851 (27.9%)	
Rest of World	513 (2.9%)	691 (3.2%)	1204 (3.1%)	
Diabetes	1632 (9.3%)	6926 (32.4%)	8558 (22.0%)	<.001
Hypertensive disease	11530 (65.7%)	18905 (88.5%)	30435 (78.2%)	<.001
History of HF	2064 (11.7%)	6688 (31.3%)	8752 (22.5%)	<.001
History of Systemic Embolism	7 (0.0%)	257 (1.2%)	264 (0.7%)	<.001
History of Liver Disease	100 (0.6%)	107 (0.5%)	207 (0.5%)	0.356
Peripheral Vascular Disease	207 (1.2%)	2005 (9.5%)	2212 (5.7%)	<.001
Carotid Artery Disease	196 (1.1%)	988 (4.7%)	1184 (3.1%)	<.001
History of Stent Use	523 (3.0%)	2041 (9.6%)	2564 (6.6%)	<.001
History of CABG	166 (1.0%)	994 (4.8%)	1160 (3.0%)	<.001
History of Stroke	80 (0.5%)	2950 (13.9%)	3030 (7.8%)	<.001
History of Alcohol Abuse	539 (3.6%)	251 (1.4%)	790 (2.4%)	<.001
History of Bleeding	295 (1.7%)	729 (3.4%)	1024 (2.6%)	<.001
History of Kidney Disease	794 (5.3%)	3244 (17.5%)	4038 (12.0%)	<.001
NSAID or Cox-2 Inhibitor	4611 (26.2%)	6579 (30.8%)	11190 (28.7%)	<.001
Initial antithrombotic				
Antiplatelet	5757 (32.8%)	8327 (39.0%)	14084 (36.2%)	<.001
New Oral Anticoagulant	3896 (22.2%)	4908 (23.0%)	8804 (22.6%)	0.064

	CHA ₂ DS ₂ -VASc 0-2 [men] or 1-3 [women] N=17566	Remaining cohort N=21369	Overall N=38935	P-Value
Vitamin K Antagonist	6682 (38.0%)	9809 (45.9%)	16491 (42.4%)	<.001
Median with 25th, 75th percentiles for continuous variables, N (%) for categorical				
History of Liver Disease	100 (0.6%)	107 (0.5%)	207 (0.5%)	0.356
Peripheral Vascular Disease	207 (1.2%)	2005 (9.5%)	2212 (5.7%)	<.001
Carotid Artery Disease	196 (1.1%)	988 (4.7%)	1184 (3.1%)	<.001
History of Stent Use	523 (3.0%)	2041 (9.6%)	2564 (6.6%)	<.001
History of CABG	166 (1.0%)	994 (4.8%)	1160 (3.0%)	<.001
History of Stroke	80 (0.5%)	2950 (13.9%)	3030 (7.8%)	<.001
History of Alcohol Abuse	539 (3.6%)	251 (1.4%)	790 (2.4%)	<.001
History of Bleeding	295 (1.7%)	729 (3.4%)	1024 (2.6%)	<.001
Kidney Disease	794 (5.3%)	3244 (17.5%)	4038 (12.0%)	<.001
Medication at baseline	17076 (97.2%)	20678 (96.8%)	37754 (97.0%)	0.011
NSAID or Cox-2 Inhibitor				
Initial antithrombotic				
Antiplatelet	5757 (32.8%)	8327 (39.0%)	14084 (36.2%)	<.001
New Oral Anticoagulant	3896 (22.2%)	4908 (23.0%)	8804 (22.6%)	0.064
Vitamin K Antagonist	6682 (38.0%)	9809 (45.9%)	16491 (42.4%)	<.001

Supplementary Table 4. Evaluation of performance (C statistic [95% Jack-knife confidence intervals]) of the full GARFIELD-AF risk model compared with CHA₂DS₂-VASc in predicting ischaemic stroke/systemic embolism (SE) in patients enrolled in ORBIT-AF (overall and stratified with and without OAC treatment)

	GARFIELD-AF risk model	CHA₂DS₂-VASc	Events n/N
1-yr Ischaemic stroke/SE	0.69 (0.64-0.75)	0.69 (0.64-0.74)	91/9743
Treated	0.66 (0.59-0.73)	0.67 (0.61-0.73)	64/7442
Untreated	0.76 (0.68-0.84)	0.75 (0.68-0.82)	27/2301
3-yr Ischaemic stroke/SE	0.67 (0.63-0.71)	0.67 (0.64-0.71)	208/9743
Treated	0.66 (0.61-0.70)	0.67 (0.63-0.71)	157/7442
Untreated	0.70 (0.63-0.77)	0.69 (0.63-0.76)	51/2301

OAC, oral anticoagulant; SE, systemic embolism

Supplementary Table 5. Evaluation of performance (C statistic [95% Jack-knife confidence intervals]) of the GARFIELD-AF risk model compared with ATRIA score in predicting major bleed in patients on OAC treatment enrolled in ORBIT-AF

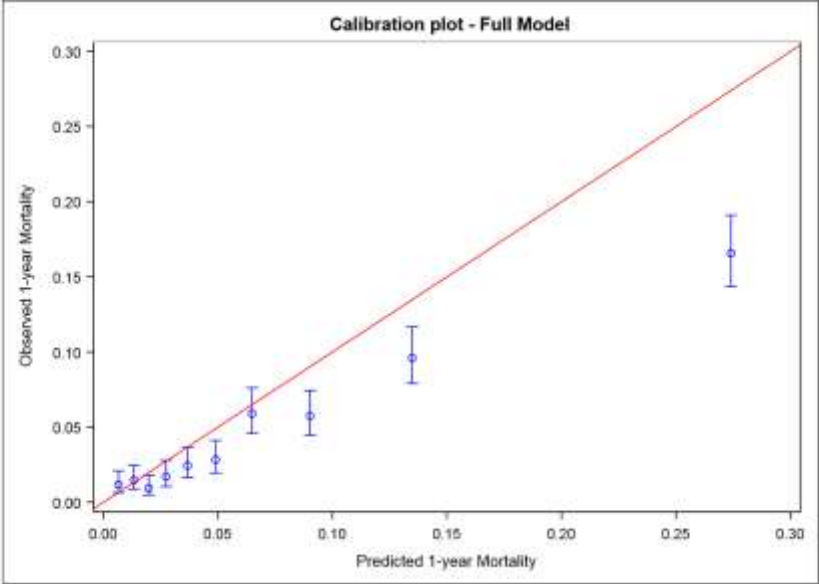
	GARFIELD-AF risk model	ATRIA score	Events n/N
1-yr Major bleed (treated patients)	0.61 (0.58-0.64)	0.65 (0.62-0.68)	305/7442
3-yr Major bleed (treated patients)	0.61 (0.59-0.63)	0.65 (0.62-0.67)	625/7442

The C-index is calculated within 1 or 3 years, using the C-index for time-to-event data (some patients have censored follow-up prior to the target horizon). Confidence intervals are based on an approximate jack knife. Most patients in ORBIT have 1 year follow-up, and many have 3 years follow-up

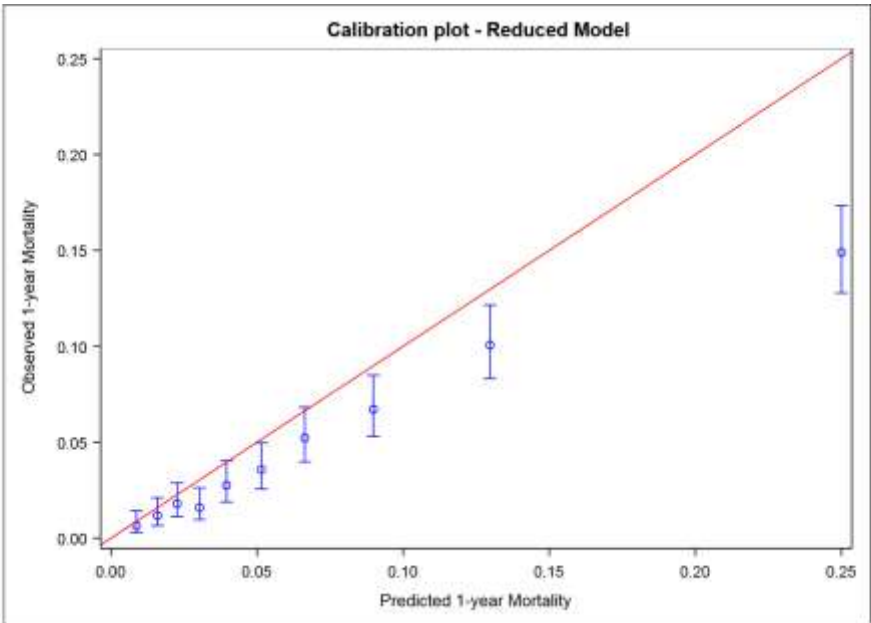
2186 patients were followed to 3 years; 1215 died before reaching the 3 year time point and 6348 were censored as alive before the 3 year.

Supplementary Figure 1. Calibration of the simplified GARFIELD-AF risk model in ORBIT-AF for a. 1 yr ischaemic stroke/SE; b. 1-yr major bleed (treated patients)

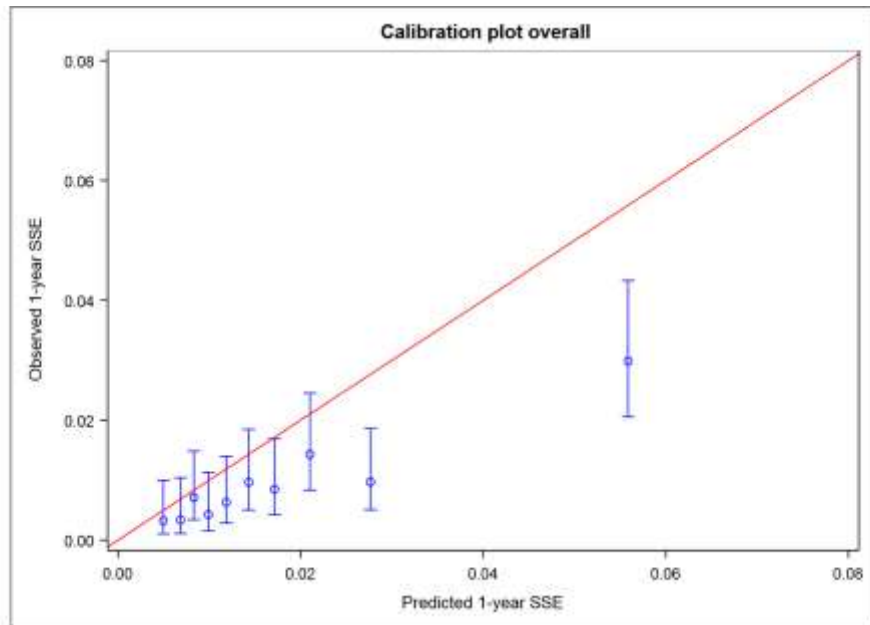
a. 1 yr mortality – Full model



b. 1 yr mortality- Reduced model



c. 1 yr ischaemic stroke/SE



d. 1-yr major bleed (treated patients)

