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GARFIELD-AF Model for Prediction of Stroke and Major Bleeding in Atrial Fibrillation: A Danish Nationwide Validation Study

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Abstract

Objectives: To externally validate the accuracy of the GARFIELD-AF model against existing risk scores for stroke and major bleeding risk in patients with non-valvular atrial fibrillation (AF) in a population-based cohort.

Design: Retrospective cohort study.

Setting: Danish nationwide registries.

Participants: 90,693 patients with newly diagnosed non-valvular AF were included between 2010 and 2016, with follow-up censored at 1-year.

Primary and secondary outcome measures: External validation was performed using discrimination and calibration plots. C-statistics were compared with CHA_2DS_2VASc for ischemic stroke/systemic embolism (SE) and HAS-BLED for major bleeding/hemorrhagic stroke outcomes.

Results: Of the 90,693 included, 51,180 patients received oral anticoagulants (OAC). Overall median age (Q1, Q3) were 75 (66-83) years and 48,486 (53.5%) were male. At 1-year follow-up, a total of 2,094 (2.3%) strokes/SE, 2,642 (2.9%) major bleedings and 10,915 (12.0%) deaths occurred. The GARFIELD-AF model was well calibrated with the predicted risk for stroke/SE and major bleeding. The discriminatory value of GARFIELD-AF risk model was superior to CHA_2DS_2VASc for predicting stroke in the overall cohort (C-index:0.71,95%-confidence interval (CI):0.70-0.72 versus C-index:0.67,95%-CI:0.66-0.68, p<0.001) as well as in low-risk patients (C-index:0.64,95%-CI:0.59-0.69 versus C-index:0.57,95%-CI:0.53-0.61, p=0.007). The GARFIELD-AF model was comparable to HAS-BLED in predicting the risk of major bleeding in patients on OAC therapy (C-index:0.64,95%-CI:0.63-0.66 versus C-index:0.64,95%-CI: 0.63-0.65, p=0.60).

Conclusion: In a nationwide Danish cohort with non-valvular AF, the GARFIELD-AF model adequately predicted the risk of ischemic stroke/SE and major bleeding. Our external validation confirms that the

GARFIELD-AF model was superior to CHA_2DS_2VASc in predicting stroke/SE and comparable with HAS-BLED for predicting major bleeding.

Strengths and limitations of this study

- This validation study was able to compare prediction performance GARFIELD-AF model versus CHA_2DS_2VASc for stroke and HAS-BLED for major bleeding in patients with atrial fibrillation.
- This study used a large contemporary population-based cohort with atrial fibrillation with many events and very limited loss to follow-up.
- The validation was based on ICD-10 coding from the Danish registries which is prone to misclassification bias and lacked clinical measurements.

INTRODUCTION

Atrial fibrillation (AF) is a common cardiac arrhythmia with a lifetime prevalence of 20-30% and is the cause of one in four strokes. [1] AF is associated with an increased risk of several cardiovascular conditions, most notably a nearly 5-fold increased stroke risk. [2, 3] The risk of stroke can be substantially diminished by thrombotic prophylaxis. [4, 5] However, 20-40% of potentially eligible patients do not receiving oral anticoagulant (OAC) therapy. [6-8] The most important and modifiable contributing factor is inappropriate risk assessment, with underutilization of existing risk scores, resulting in overestimation of bleeding risks and underestimation of potential stroke risk. [9, 10] Recently, the Global Anticoagulant Registry in the FIELD –Atrial Fibrillation (GARFIELD-AF) model was developed that allowed for simultaneous calculation of death, stroke, and bleeding risks in an international prospective registry of patients with newly diagnosed AF. [11] In the GARFIELD-AF and ORBIT-AF registries, the GARFIELD-AF model was found to improve discrimination of the existing risk scores for stroke (CHA_2DS_2-VASc) and bleeding (HAS-BLED). [11-13] These registries may not cover the full spectrum of patients with AF, which warrants external validation of these risk scores in other population-based cohorts. We aimed to 1) externally validate the GARFIELD-AF model of ischemic stroke and major bleeding outcomes among patients with newly diagnosed AF in a large contemporary Danish cohort and 2) perform a head-to-head comparison of the predictive properties of GARFIELD-AF model with CHA_2DS_2-VASc for thromboembolic events and HAS-BLED for major bleeding. We did not externally validate the GARFIELD-AF model for risk of death, as we did not have blood pressure and heart rate measurements; covariates that the GARFIELD-AF model for death requires.

MATERIALS AND METHODS

We reported our findings according to the TRIPOD (Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis) criteria. [14]

Data sources

We used the Danish nationwide registers cross-linking The Civil Registration System, The Danish National Patient Register (DNPR), and The Danish Drug Statistical Registry. The Civil Registration

System holds data on age, sex, and vital status. DNPR contains all hospital admissions according to ICD-10 and procedures. The Danish Drug Statistical Registry was used to characterize pharmacotherapy in which all claimed drug prescriptions are registered. To compare characteristics (baseline and outcomes) of the Danish registry we used data from the GARFIELD-AF registry which, in brief, is an observational, multicentre, international study of newly diagnosed AF with ≥1 risk factor for stroke. [15]

Study population

From the DNPR, patients aged ≥18 years with a primary or secondary diagnosis of AF or atrial flutter (International Classification of Diseases, Tenth Revision [ICD-10]: I48), hospitalization or outpatient visit, were included from January 1, 2010 until August 1st 2016 with follow-up to August 1st 2017. The diagnosis of AF in the DNPR has a positive predictive value of 94.0%. [16] Patients with rheumatic valvular heart disease or valve interventions were excluded. To allow patients time to fill their prescriptions after discharge, a 10-day wash-out period was used. Due to no data on race/ethnicity in the The Civil Registration System, we excluded immigrants and those with missing information on immigration and presumed Caucasian/European-white for non-immigrants. Given complete nationwide coverage of DNPR missing data is not present. For baseline characteristic and outcome comparison, we included the worldwide enrolled GARFIELD-AF patients and the patients enrolled from the Scandinavian sites; Denmark, Sweden, Norway, Finland (GARFIELD-AF Scandinavia).

Covariates, GARFIELD-AF model, CHA_2DS_2-VASc, and HAS-BLED

For the Danish AF cohort, all baseline variables were defined from ICD-10 codes, as any primary or secondary diagnosis, inpatient or outpatient, registered up to 10 years prior to the inclusion date. Pharmacotherapy at baseline was identified by Anatomical Therapeutic Chemical (ATC) codes of prescription drugs claimed up to 180 days prior to the inclusion date. For oral anticoagulants, within the 180 days the latest prescription filled of either vitamin K antagonist (VKA) or non-vitamin K oral anticoagulants (NOAC) was used. Prescriptions claimed for anti-diabetic drugs were used as proxy for diabetes mellitus. Hypertension was defined as claimed prescription for a combination of at least two of the seven different antihypertensive drugs classes as previously reported. [17] The algorithm for GARFIELD-AF 1-year risk of ischemic stroke/systemic embolism (SE) relies on the following variables:

age (in years), history of ischemic stroke, prior bleeding (any recorded in medical records), heart failure (medical history of heart failure, or ejection fraction of <40%), chronic kidney disease (CKD) (stage III-V), race/ethnicity, and use of oral anticoagulant (VKA or NOAC). The algorithm for GARFIELD-AF 1-year risk of major bleeding/haemorrhagic stroke was developed in patients taking OAC and involves age, chronic kidney disease (CKD), and vascular disease, in which the latter is defined as history of myocardial infarction (MI) or unstable angina, aortic, or peripheral artery disease. The CHA_2DS_2-VASc score is composed of age, sex, a history of heart failure, hypertension, stroke, transient ischemic attack (TIA), thromboembolism, and/or diabetes. HAS-BLED is composed of age, uncontrolled hypertension, renal disease, liver disease, labile international normalized ratio (INR), medication use predisposing to bleeding, and a history of stroke, major bleeding and/or predisposition to bleeding. All covariates were based on ICD-10 codes. The equations for these respective scores and ICD-10 codes can be found in *Table S1*.

Definitions of end points

The primary efficacy endpoint for this study involved a 1-year composite of ischemic stroke or SE. The primary safety endpoint involved a composite of haemorrhagic stroke or major bleeding. Major bleeding was defined as an organ-specific bleeding requiring hospitalization. [18] A list of ICD-10 codes used to compute these definitions can be found in *Table S2.* In the GARFIELD–AF cohorts, the occurrence of 'major bleeding' was defined according to the International Society on Thrombosis and Haemostasis (ISTH) criteria. [11, 15, 19]

Patient and public involvement

Patients or the public were not involved in the design of the study

Statistical Analyses

For the Danish AF cohort, we stratified baseline characteristics by CHA_2DS_2-VASc score (≤2 for women, 0-1 for men and >2 for women and >1 for men). The Danish AF cohort were followed for a maximum of 1 year from the discharge date and until the event of interest (stroke/SE or major bleeding), death, emigration or end of follow-up (August, 2017). For all three cohorts (Danish AF cohort, GARFIELD Scandinavia, GARFIELD global), 1-year absolute risks of stroke/SE and major

bleeding were estimated non-parametrically using the Aalen-Johansen estimator with competing risk of death. For the Danish AF cohort, using a logistic regression model we used the original coefficients from the GARFIELD-AF model development study. The discriminative performance of GARFIELD-AF for predicting ischemic stroke/SE and major bleeding hospitalizations was assessed using receiver operating characteristics (ROC) curves and reported as area under the curve (AUC) values. The C-index with 95% confidence intervals (CI) was reported as a measure of discrimination and tested for significance with DeLongs method. Calibration was assessed by calculating deciles of predicted probabilities and plotting the average predicting with the observed Kaplan-Meier rate and 95% CI within each decile. A subgroup analysis for stroke prediction was undertaken for low risk patients. As a sensitivity analysis, we estimated the logistic regression coefficients for each individual covariate used in the GARFIELD-AF models. Statistical analyses were performed using R software (Team RC. R: A Language and Environment for Statistical Computing. 2019).

RESULTS

From the Danish registries, a total of 110,276 patients were diagnosed with AF between 2010 and 2016. Of those patients, 91,836 met the inclusion criteria for the study (Figure S1). Of these, 70,020 were identified as high risk and 20,673 was identified as low risk of stroke/SE. A total of 51,180 were on OACs. From the GARFIELD-AF registries, 52,080 patients with AF were included globally, and 2,396 patients were included from the Scandinavian sites.

Characteristics of study participants

Baseline characteristics for all three cohorts (Danish AF cohort, GARFIELD Scandinavia, GARFIELD global) are shown on Table 1. Compared to GARFIELD Scandinavia, the Danish AF cohort had a more equal representation of men and women (54% vs 58%) and was older (median age 75 vs 73). There were also notable differences in comorbidities, in which diabetes, hypertension, and chronic kidney disease were less prevalent in the Danish AF cohort, whereas a history of bleeding (11.6% vs 1.9% vs. 2.5%) was much more prevalent compared with the GARFIELD Scandinavia or global cohorts. Despite these differences the median CHA_2DS_2Vasc scores were comparable among all cohorts but the HAS-BLED median was higher in the Danish AF cohort. For the GARFIELD model, the median GARFIELD scores were higher in the Danish AF cohort than both GARFIELD cohorts. The

use of OAC therapy was 56.4% in the Danish AF cohort, which was lower than the reported percentages in GARFIELD Scandinavia (68.0%) and GARFIELD global (60.8%). The use of aspirin, ADP-inhibitors and NSAIDs was higher in the Danish AF cohort. The characteristics of patients at low (CHA_2DS_2Vasc of 0-1 in men and 1-2 in women; n=20,673) and high risk (n=70,020) for the Danish AF population is displayed in Table S3. The median [IQR] for CHA_2DS_2-VASc and HAS-BLED scores in the high-risk group were 4 [3-5] and 2 [2-3].

Clinical outcomes at 1-year Follow-up

Table 2 displays the number of stroke/SE, major bleeding, and all-cause mortality for the Danish AF cohort. Over a 1-year follow-up period, a total of 2,094 (2.3%) stroke/SE, 2,642 (2.9%) major bleedings were reported. Annual mortality rates were high with 10,915 deaths (11.9 per 100 person years). For the OAC treated patients there were 4,521 deaths (8.8 per 100 person years) and for low risk patients there were 623 deaths (3.0 per 100 person years). The cumulative incidence for ischemic stroke to 1-year for low and high-risk patients are presented in Figure S2 for the Danish AF cohort. The cumulative incidence of stroke/systemic embolism and ischemic stroke for the Danish AF cohort, GARFIELD Scandinavia, and GARFIELD Global can be found in Figure 1.

External validation of GARFIELD-AF model

The C-index for the GARFIELD-AF model for 1-year stroke was 0.71 (95%-CI: 0.70-0.72) in the overall Danish AF cohort of 90.693 patients and 0.64 (95%-CI: 0.59-0.69) in low-risk patients not requiring OAC therapy (n=20,673). The C-index for the GARFIELD-AF model for 1-year major bleeding risk was 0.64 (95%-CI 0.63-0.66) in patients using OAC therapy. The GARFIELD-AF model for stroke/SE and major bleeding scores were both well calibrated in the Danish AF cohort (Figure 2 and 3). The individual covariates in the GARFIELD-AF model expressed a similar regression coefficient for most covariates in the Danish cohort when compared with the original derivation GARFIELD-AF cohort (Table S4).

GARFIELD-AF model versus CHA_2DS_2-VASc score for predicting stroke/SE

The AUC curves for predicting stroke using the GARFIELD model and CHA_2DS_2-VASc scores are displayed in Figure 4. The AUC and corresponding C-index for GARFIELD was significantly higher

when compared with CHA_2DS_2Vasc for predicting stroke outcomes, in the overall cohort (C-index: 0.71, 95%-CI: 0.70-0.72 versus 0.67, 95%-CI: 0.66-0.68) as well as in low-risk patients (C-index: 0.62, 95%-CI: 0.59-0.69 versus 0.57, 95%-CI: 0.53-0.61).

GARFIELD-AF model versus HAS-BLED score for predicting major bleeding/haemorrhagic stroke

Figure 4C illustrates the AUC curves for the prediction of major bleeding based on the GARFIELD and HAS-BLED scores in patients taking OAC therapy. The discriminatory value of GARFIELD was comparable with HAS-BLED: C-index: 0.64 (95%-CI: 0.63-0.66) versus C-index: 0.64 (95%-CI: 0.63-0.65), respectively.

Table 3 displays available evidence comparing the discriminatory properties of various models for stroke/SE and major bleeding.

Discussion

In a large unselected contemporary Danish AF cohort, our study demonstrates that the GARFIELD-AF model serves as a reliable risk stratification tool. We found that the GARFIELD-AF model surpasses the widely used CHA_2DS_2-VASc score in predicting the risk of stroke, both in high and low-risk patients. For predicting major bleeding, the three-item GARFIELD-AF model is on par with HAS-BLED among anticoagulated patients with AF.

Risk-stratification of patients with AF is essential to mitigate the risk of stroke/SE when initiating anticoagulation therapy. As such, the easy-to-calculate CHA_2DS_2-VASc score serves as the risk-stratification tool recommended by international guidelines to commence therapy when the risk of stroke reaches a threshold of >2% per annum. [20] Prior studies have shown that guideline-adherent (risk-stratified) anticoagulation therapy is associated with a 60-70% reduction in thromboembolic associated complications and mortality. [21] Despite these reductions in stroke risk, there is still room for improvement in risk stratification of patients with AF and anticoagulation therapy. In this regard, the GARFIELD-AF model, which calculates the risk of stroke, death, and major bleeding, is promising, particularly as it performed better than the CHA_2DS_2-VASc and HAS-BLED. [11] The GARFIELD-AF model provides estimates of the risk of stroke/SE and bleeding (and mortality when blood pressure

and heart rate data are available) in a single calculation and based on routinely collected data would have potentially wide clinical applications.

Underuse of anticoagulation therapy is a well-known problem in particular in high-risk patients. [22] Our study found that 73.1% of patients with increased stroke risk (n=51,180, CHA_2DS_2-VASc>2 in women and >1 in men) received anticoagulation therapy. Studies suggests that treatment barriers are based on overestimation of bleeding risks (for example recurrent falls and prior peptic ulcers) and lack of reliable risk stratification tools and readily available information that does not rely on specific lab tests such as HAS-BLED. [9, 10, 22]

To provide predictions for bleeding risk, several bleeding scores have been developed, of which HAS-BLED has been most rigorously tested. [23, 24] While the HAS-BLED risk score is clinically useful to identify patients at high bleeding risk, it requires information that may not always be available in outpatient and primary care settings, such as information on liver function tests, INR status, and presence of anemia. This may be a limitation for the implementation of this score in low-resource settings and is of relevance as the majority (60%) of community-dwelling patients with AF are seen in primary care. [25, 26] Moreover, primary care physicians achieve lower anticoagulation rates compared with hospital-based physicians. [27, 28] While there are multiple reasons for these differences, which include differences in populations, with high percentage of (relative) contraindications (40-65%) and care-related factors, the lack of an integral decision tool impedes informed decisions on initiating or continuing antithrombotic therapy. [10, 29]

In the present study, the external validation show that GARFIELD-AF is well calibrated with the predicted risks, and the good calibration aligns well with the original GARFIELD-AF derivation cohort. [11] GARFIELD-AF score has improved discriminatory abilities compared to CHA_2DS_2-VASc score in stroke prediction and on par with HAS-BLED for bleeding prediction. To our surprise, our external validation of GARFIELD-AF discriminatory c-index for stroke prediction was slightly higher (0.71) than the c-index in the original GARFIELD cohort (0.69). Furthermore, the Danish AF cohort were older with more stroke events than both GARFIELD cohorts and higher predicted risk than the GARFIELD cohorts. The opposite was the case for major bleeding prediction where the original GARFIELD cohort had better discriminatory abilities than HAS-BLED. The significant differences in the cohort characteristics, for example higher HAS-BLED and more use of combined OACs and

antiplatelet therapy in the Danish AF cohort, and definitions of covariates and outcomes are likely to play a key role in both instances.

The value of CHA_2DS_2-VASc score in defining patients with a truly low risk of stroke is uncertain, partly because the number of patients to accurately assess lower risk patients in the original studies was insufficient. [12, 30] The evaluation of the performance of risk scores in this low-risk category is important, as it determines the threshold when initiating antithrombotic therapy outweighs the risk of bleeding. In our study we found that the GARFIELD-AF model for low risk patients was well calibrated and provided a better prediction than CHA_2DS_2-VASc score in indicating which patients are truly at low-risk for subsequent stroke.

Limitations and future directions

The primary limitation of this study is that definitions are based on administrative ICD-10 codes which are prone to random misclassification bias. Discrepancies exist between the GARFIELD-AF registry and the Danish registries in the definitions of comorbidities and clinical outcome data. This was most notable for major bleeding and stroke/SE events and CKD. In the Danish AF cohort, selected ICD-10 codes for bleeding hospitalizations were applied, whereas GARFIELD-AF applied the ISTH criteria for major bleeding, which are more restrictive. Apart from differences in disease definitions, the relative high number of bleeding and stroke/SE events in the Danish AF cohort could also be explained by site of enrollment (only hospital/outpatient). Similar data limitations apply to the construction of CHA_2DS_2-VASc score and HAS-BLED scores which was calculated from ICD-10 code usage although this study followed the standards set by other researchers using the same Danish registries [17]. Specifically, we were unable to account for labile INR component of the HAS-BLED score. Another limitation was the inability to ascertain ethnicity status which is an integrated covariate of the GARFIELD-AF model. Therefore, we excluded immigrants to strengthen the assumption of European/Caucasian ethnicity in the cohort. The GARFIELD Scandinavian cohort consisted of 99.3% Caucasians. Population-based studies in other more ethnically-diverse cohorts are warranted. For the implementation of the GARFIELD-AF model, an online risk calculator already exist. A next step would be to provide an electronic health record integrated solution, in which stroke/SE and bleeding risks are automatically calculated when a patient is identified with AF. Doing so, would promote balanced and evidence-based decision making on anticoagulation therapy. Integrating the GARFIELD-AF model into

electronic health records would also provide a way for anonymous monitoring of outcomes of patients in which the GARFIELD-AF model was applied, which can be used to further optimize risk prediction.

Conclusion

The GARFIELD-AF model adequately predicted the risk of ischemic stroke/SE and major bleeding/haemorrhagic stroke in a nationwide Danish cohort of contemporary patients with non-valvular AF. Our external validation confirms that the performance of the GARFIELD-AF model was superior to CHA_2DS_2VASc in predicting stroke/SE both in high-risk and in low risk patients and comparable with HAS-BLED for predicting major bleeding. The GARFIELD-AF model holds an advantage over the existing risk scores as it permits for simultaneous evaluation of death, stroke and bleeding risks and uses readily available clinical parameters. As such, the tool may lead to more informed treatment decisions, improve monitoring for bleeding complications, and improve outcomes for patients treated for AF in the community.

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Conflicts of interests:

KAAF: has received research grants Bayer/Janssen and AstraZeneca and Consulting/Fees Bayer, Sanofi/Regeneron and Verseon

FWAV: has received honoraria for consulting and presentations from Bayer HealthCare, Boehringer Ibgelheimy, BMSPfizer and Daiichi-Sankyo

GG: has ownership of stocks in Novo Nordisk Pharmaceuticals and reports research grants from Pfizer, Bristol Myers Squibb, Boehringer Ingelheim and Bayer.

CTP: declares grants for studies from Bayer.

Other authors have no conflicts of interest to declare

Patient consent:

Obtained

Ethics approval:

For the GARFIELD-AF registry an independent ethics committee and hospital-based institutional review board approvals were obtained for the registry protocol. In Denmark, retrospective register studies do not require approval from the ethics committees. The Danish Data Protection Agency approved this study (Ref no: 2007-58-0015, I-Suite nr: 02732, GEH-2014-014). Data were made available in an anonymized format such that specific individuals could not be identified.

Contributors:

FD, REH, MR, FWAV, KAAF, AKK, HVW and KP contributed to the study concept and design; FD, and KP conducted the data analysis; REH and FD and drafted the manuscript; all authors critically reviewed the final draft of the manuscript.

Data sharing statement:

Due to restrictions related to Danish law and protecting patient privacy, the combined set of data as used in this study can only be made available through a trusted third party, Statistics Denmark. This state organisation holds the data used for this study. Any request on data access should be addressed to Statistics Denmark https://www.dst.dk/en.aspx#

Table 1. Baseline characteristics of patients from the Danish AF cohort, GARFIELD-AF Scandinavia, and GARFIELD-AF Global registries

	Danish AF cohort	**GARFIELD-AF Scandinavia**	**GARFIELD-AF Global**
n	90693	2396	52080
Age (median [IQR])	75 [66.0, 83.0]	73.0 [66.0, 78.0]	71.0 [63.0, 78.0]
Sex, male (%)	48486 (53.5)	1389 (58.0)	29068 (55.8)
Race, Caucasian (%)	NA	1860 (99.3)	32028 (63.1)
Diabetes (%)	10900 (12.0)	387 (16.2)	11555 (22.2)
Stroke/TIA (%)	12827 (14.1)	325 (13.6)	3879 (7.5)
Systemic embolism (%)	448 (0.5)	6 (0.3)	335 (0.6)
History of bleeding (%)	10544 (11.6)	46 (1.9)	1318 (2.5)
Vascular disease (%)	15305 (16.9)	268 (11.2)	7682 (14.8)
Chronic kidney disease (%)	4224 (4.7)	185 (7.7)	5360 (10.3)
Heart Failure (%)	14961 (16.5)	348 (14.5)	11758 (22.6)
Ischemic heart disease (%)	13445 (14.8)	331 (13.8)	11265 (21.6)
Hypertension (%)	55665 (61.4)	1659 (69.4)	39643 (76.3)
VTE or PE (%)	5141 (5.7)	77 (3.2)	1355 (2.6)
NOAC (%)	23212 (25.6)	521 (21.7)	11004 (21.1)
VKA (%)	27968 (30.8)	1110 (46.3)	20708 (39.8)
OAC (%)	51180 (56.4)	1631 (68.0)	31712 (60.8)
VKA + AP (%)	10773 (11.9)	181 (7.6)	4827 (9.4)
NOAC + AP (%)	7608 (8.4)	47 (2.0)	1896 (3.7)
NSAID (%)	13078 (14.4)	23 (1.0)	1701 (3.3)
Acetylsalicylic acid (%)	32890 (36.3)	413 (17.2)	14636 (28.1)

ADP-inhibitor (%)	9128 (10.1)	89 (3.7)	3580 (6.9)
CABG (%)	3291 (3.6)	92 (3.9)	1625 (3.2)
CHA_2DS_2VASC (median [IQR])	3.0 [2.0, 4.0]	3.0 [2.0, 4.0]	3.0 [2.0, 4.0]
CHA_2DS_2VASC (%)			
0	5678 (6.3)	19 (0.8)	1516 (2.9)
1	10231 (11.3)	279 (11.7)	6369 (12.4)
2	16137 (17.8)	530 (22.2)	10230 (19.9)
3	20143 (22.2)	626 (26.2)	12138 (23.6)
4	19378 (21.4)	526 (22.1)	11022 (21.4)
5	11020 (12.2)	238 (10.0)	5895 (11.5)
>5	8106 (8.9)	167 (7.0)	4238 (8.2)
HAS-BLED (median [IQR])	2.0 [1.0, 3.0]	1.0 [1.0, 2.0]	1.0 [1.0, 2.0]
HAS-BLED category n, missing (%)		1088 (1308)	37549 (14531 - missing)
0	8297 (9.1)	169 (15.5)	5471 (14.6)
1	19956 (22.0)	507 (46.6)	16169 (43.1)
2	31170 (34.4)	301 (27.7)	11692 (31.1)
3	24998 (27.6)	87 (8.0)	3570 (9.5)
>3	6272 (6.9)	24 (2.2)	647 (1.7)
GARFIELD-AF model, stroke, median (IQR)	1.10 [0.75, 1.82]	0.80 [0.60, 1.10]	0.90 [0.70-1.40]
GARFIELD-AF model, bleed, median (IQR)	1.08 [0.74, 1.54]	0.90 [0.70,1.30]	1.00 [0.70-1.40]

Table 1 footnotes. Abbreviations: TIA; transient ischemic attack, SE; systemic embolism, OAC; oral anticoagulants, NOAC; non-vitamin-K antagonist, VKA; vitamin-K antagonist; AP; anti-platelet therapy, NSAID; non-steroidal anti-inflammatory drug, ADP; adenosine diphosphate, CABG; Coronary Artery Bypass Grafting.

Table 2. Number of events (Stroke/SE, major bleed) and deaths for one 1-year follow-up in all patients, patients on OAC, and low risk patients

	Danish AF cohort (n=90693)	Patients treated with OAC (n=51180)	Low risk patients (n=20673)
Stroke	2094	994	139
Major bleeding	2642	1492	242
Deaths	10915	4521	623

Table 2 footnotes. Low risk patients were defined as CHA_2DS_2-VASc score (≤2 for women, 0-1 for men and >2 for women and >1 for men). Abbreviations: OAC; oral anticoagulation.

Table 3. Available evidence comparing the discriminatory properties of various models for stroke/SE and major bleeding [11, 23]

Outcome	Cohort	N	GARFIELD-AF - AUC (95% CI)	CHA_2DS_2-VASc /HAS-BLED - AUC (95% CI)
Stroke/SE	GARFIELD-AF	39,898	0.69 (0.67-0.71)	0.64 (0.61-0.66)
	ORBIT-AF	9,743	0.69 (0.64-0.75)	0.69 (0.64-0.74)
	Danish AF cohort	90,693	0.71 (0.70-0.72)	0.67 (0.66-0.68)
Stroke/SE low risk patients	GARFIELD-AF	7,882	0.65 (0.56-0.73)	0.59 (0.50-0.67)
	Danish AF cohort	20,673	0.64 (0.59-0.69)	0.57 (0.53-0.61)
Major bleeding	GARFIELD-AF	25,677	0.66 (0.62-0.69)	0.64 (0.61-0.68)
	ORBIT-AF	7,442	0.61 (0.58-0.64)	-
	SPORTIF III-V	3,550	0.56 (0.54-0.57)	0.58 (0.56-0.60)
	Danish AF cohort	51,180	0.64 (0.63-0.66)	0.64 (0.63-0.65)

Figure 1.

Figure 1 legend. Cumulative incidence of stroke/systemic embolism (panel A) and major bleeding (panel B) in the Danish AF cohort, GARFIELD-AF Scandinavia, and GARFIELD-AF Global.

Figure 2.

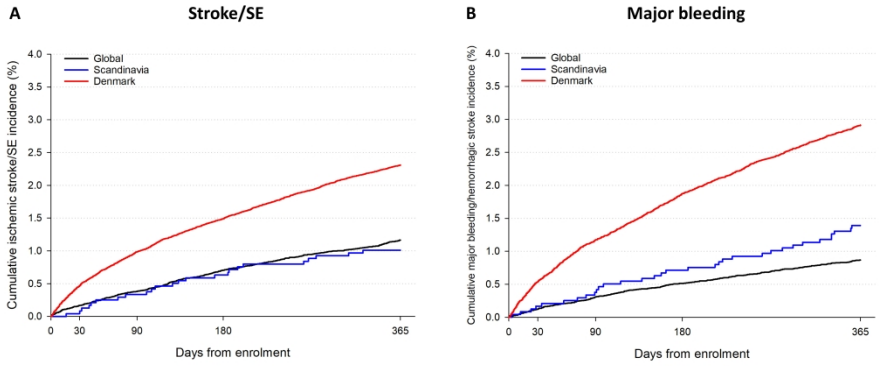
Figure 2 legend. Calibration plots of GARFIELD-AF model and stroke/SE risk in overall Danish population (A) and in low-risk patients (B). Predicted probability for GARFIELD (blackline), and actual observed cumulative incidence estimates with 95% CI for each GARFIELD score in deciles including a linear regression model (dashed line) and LOESS function of observed probability (red line).

Figure 3.

Figure 3 legend. Calibration plots of GARFIELD-AF model and major bleeding risk in Danish population. Predicted probability for GARFIELD (blackline), and actual observed cumulative incidence estimates with 95% CI for each GARFIELD score in deciles including a linear regression model (dashed line) and LOESS function of observed probability (red line).

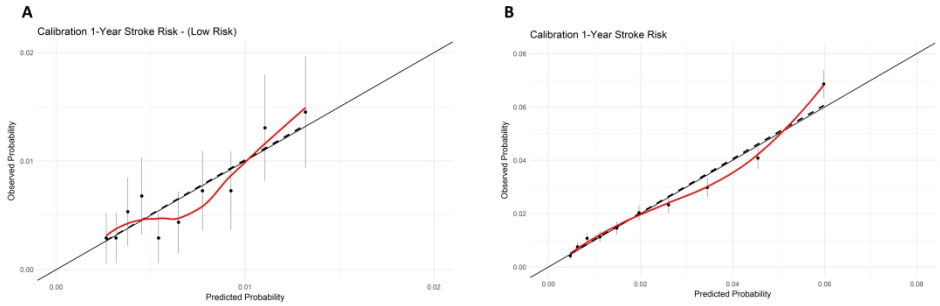
Figure 4.

Figure 4 legend. Receiver Operating Characteristic curves of GARFIELD-AF model versus CHA_2DS_2VASc scores for predicting stroke in (A) the Danish AF cohort and (B) low-risk individuals and (C) GARFIELD-AF model versus HAS-BLED scores for predicting major bleeding in the Danish AF cohort in those receiving oral anticoagulants (n=51,180). Low risk stroke patients were defined as CHA_2DS_2-VASc score (≤2 for women, 0-1 for men and >2 for women and >1 for men).



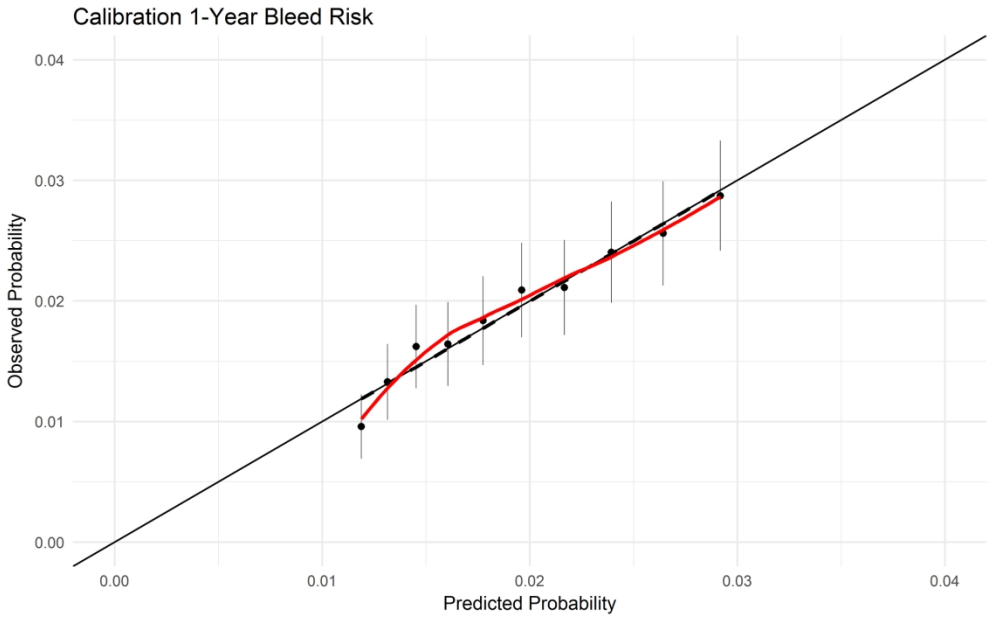
Cumulative incidence of stroke/systemic embolism (panel A) and major bleeding (panel B) in the Danish AF cohort, GARFIELD-AF Scandinavia, and GARFIELD-AF Global.

338x190mm (300 x 300 DPI)



Calibration plots of GARFIELD-AF model and stroke/SE risk in overall Danish population (A) and in low-risk patients (B). Predicted probability for GARFIELD (blackline), and actual observed cumulative incidence estimates with 95% CI for each GARFIELD score in deciles including a linear regression model (dashed line) and LOESS function of observed probability (red line).

350x170mm (300 x 300 DPI)



Predicted probability for GARFIELD (blackline), and actual observed cumulative incidence estimates with 95% CI for each GARFIELD score in deciles including a linear regression model (dashed line) and LOESS function of observed probability (red line).

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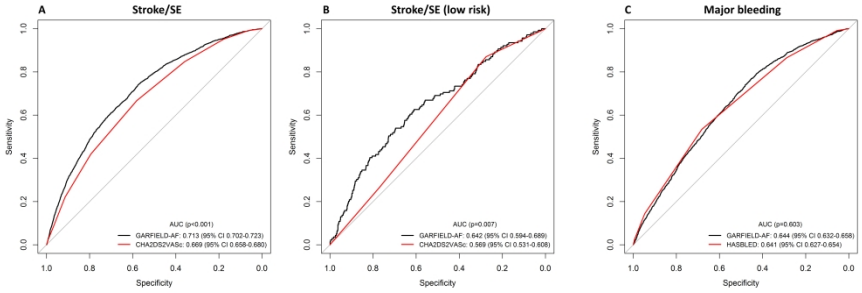

Receiver Operating Characteristic curves of GARFIELD-AF model versus CHA2DS2VASc scores for predicting stroke in (A) the Danish AF cohort and (B) low-risk individuals and (C) GARFIELD-AF model versus HAS-BLED scores for predicting major bleeding in the Danish AF cohort in those receiving oral anticoagulants (n=51,180). Low risk stroke patients were defined as CHA2DS2-VASc score (≤2 for women, 0-1 for men and >2 for women and >1 for men).

520x180mm (300 x 300 DPI)

SUPPLEMENTAL DATA FILE

Table S1. Equations of the risk scores

GARFIELD-AF stroke/SE (original)	100*(1-(0.991344397**(exp(0.0304823*(Age-60) + 0.952524717* stroke/TIA/SE + 0.432357326*Bleeding + 0.319129628* Heart failure + 0.574919171* Chronic kidney disease + 0.654249546*other region + 0.671380382*race- 0.582045773*OAC))))
GARFIELD-AF stroke/SE (modified for this analysis)	100*(1-(0.991344397**(exp(0.0304823*(Age-60) + 0.952524717* stroke/TIA/SE + 0.432357326*Bleeding + 0.319129628* Heart failure + 0.574919171* Chronic kidney disease - 0.582045773*OAC))))
GARFIELD-AF major bleeding	100*(1-(0.994488926**(exp(0.0389958*(AGE-60) + 0.515013074*vascular disease + 0.577378429* Chronic kidney disease))))
CHA_2DS_2-VASc	65≤ age <75: 1 point Age ≥75: 2 point Female sex: 1 point Heart failure: 1 point Hypertension: 1 point Ischemic stroke / TCI / Systemic embolism and thrombosis: 2 points Ischemic Heart Disease or Peripheral atherosclerosis: 1 point Diabetes: 1 point
HAS-BLED	Age >65: 1 point Hypertension: 1 point Chronic kidney disease: 1 point Liver disease: 1 point Ischemic stroke / TCI / Systemic embolism and thrombosis: 1

	points Bleeding: 1 point ASA or ADP inhibitors or Dipyridamole or NSAID: 1 point Alcohol: 1 point

Table S2. Definitions of covariates.

	ICD-10 codes
Atrial Fibrillation	I48
Non-Valvular Atrial Fibrillation	Presence of: I48 With absence of: Rheumatic heart valve disease, prostatic heart valve
Rheumatic heart valve disease	ICD10: Z952, Z954, I05, I06, I080A, I081A, I082A, I083A
Prostatic heart valve	KFKD, KFKH, KFMD, KFMH, KFGE, KFJF
Stroke / TIA / Systemic embolism and thrombosis (without hemorrhagic stroke), baseline	Ischemic: I63, I64 TIA: G458, G459 Systemic embolism and thrombosis: I74
Stroke/SE, endpoint	Ischemic: I63, I64 Systemic embolism and thrombosis: I74
Hospitalization for any bleeding, baseline	Heart: I312 Urine: N02, R31 Airways: R04 Eye: H313, H356, H431, H450, H052A Gastrointestinal: K228F, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K290, K298A, K625, K638B, K638C, K838F, K868G, K920, K921, K922, I850, I864A Intra-dural bleeds not hemorrhagic stroke: S064, S065, S066 Hemorrhagic stroke: I60, I61, I62, I690, I691, I692 Retro-peritoneal: K661 Thorax: J942 Anemia due to bleeding: D500, D62
Major bleeding (with hemorrhagic stroke)	Heart: I312 Urine; N02, R31 Eye: H313, H356, H431, H450 Airways: R04 Gastrointestinal: K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K280, K282, K284, K286, K920, K921, K922 Intra-dural bleeds not hemorrhagic stroke: S064, S065, S066, I692 Hemorrhagic stroke: I60, I61, I62, I690, I691 Thorax: J942 Retro-peritoneal: K661

	Anemia due to bleeding: D62
Heart Failure	Cardiomyopathy: I42 Heart failure: I50, I110 Lung edema: J81
IHD	Ischemic Heart Disease: I20-I25 • Angina pectoris: I20 • Acute myocardial infarction: I21, I22 • Complications to AMI: I23, • Other forms of ischemic heart disease: I24, I25
Peripheral artery disease	I70
Vascular disease	Presence of Ischemic heart disease or peripheral artery disease
Chronic Kidney Disease	N02, N03, N04, N05, N06, N07, N08, N11, N12, N14, N18, N19, N26, N158, N159, N160, N162, N163, N164, N168 Q61, E102, E112, E132, E142, I120, M321B
Pulmonary embolism	I26
Alcohol	F10, K70, E52, T51, K860, E244, G312, I426, O354, Z714, Z721, G621, G721, K292, L278A
Liver disease	B15, B16, B17, B18, B19, C22, K70, K71, K72, K73, K74, K75, K76, K77, Z944, I982, D684C
Diabetes Mellitus	Insulin: A10A Non-Insulin: A10B
OAC	VKA: Warfarin: B01AA03, Phenprocoumon: B01AA04 NOAC: Dabigatran: B01AE07, Rivaroxaban: B01AF01, Apixaban: B01AF02
Acetylsalicylic acid	B01AC06, N02BA01
ADP-inhibitors	B01AC04, B01AC24, B10AC22
NSAID	M01A without M01AX05
Hypertension as usage of combination of at least two of the seven different drugs classes at the same time.	1. Non-Loop: Thiazides C02L, C02DA, C07B, C07D, C09XA52, C03A, C03EA; Low-ceiling diuretics (excl. thiazides): C03B, C03X, C07C, C08G, C09BA, C09DA; Potassium-sparing agents (spiron): C03D, C03E,C03EB 2. Loop: High-ceiling diuretics (Loop) C03C,C03EB 3. Antiadrenergic agents: C02A, C02B, C02C

	4. Beta-blockers: C07A, C07B, C07C, C07D, C07F 5. Vasodilators: C02DB, C02DD, C02DG 6. Calcium channel blockers: C08, C09BB, C09DB 7. RASi: C09AA, C09BA, C09BB, C09CA, C09DA, C09DB, C09XA02, C09XA52

Table S3. Baseline characteristics for the Danish population, stratified by CHA_2DS_2VASC score. Low (0-1 men, 1-2 women) risk and high-risk.

	Low risk	High risk
n	20,673	70,020
age (median [IQR])	61 [54, 68]	78 [71, 85]
Sex, male (%)	13083 (63.3)	35403 (50.6)
Diabetes (%)	286 (1.4)	10614 (15.2)
Stroke/TIA (%)	0 (0.0)	12827 (18.3)
Systemic embolism (%)	0 (0.0)	448 (0.6)
History of bleeding (%)	1154 (5.6)	9176 (13.1)
Chronic kidney disease (%)	296 (1.4)	3928 (5.6)
Heart failure (%)	225 (1.1)	14736 (21.0)
Ischemic heart disease (%)	492 (2.4)	12953 (18.5)
OAC (%)	8801 (42.6)	42379 (60.5)
NOAC (%)	4307 (20.8)	18905 (27.0)
VKA (%)	4494 (21.7)	23474 (33.5)
venous thromboemobolism (%)	380 (1.8)	2301 (3.3)
Pulmonary embolism (%)	0 (0.0)	2460 (3.5)
Dipyridamole (%)	78 (0.4)	2629 (3.8)
Hypertension (%)	3601 (17.4)	52064 (74.4)
NSAID (%)	3113 (15.1)	9965 (14.2)
Acetylsalicylic acid (%)	3685 (17.8)	29205 (41.7)
ADP-inhibitor (%)	335 (1.6)	8793 (12.6)
PCI (%)	252 (1.2)	6104 (8.7)
CABG (%)	109 (0.5)	3182 (4.5)
CHA_2DS_2VASC (median [IQR])	1.0 [0.0, 1.0]	4.0 [3.0, 5.0]
CHA_2DS_2VASC (%)		
0	5678 (27.5)	-

1	10231 (49.5)	-
2	4764 (23.0)	11373 (16.2)
3	-	20143 (28.8)
4	-	19378 (27.7)
5	-	11020 (15.7)
>5	-	8106 (11.6)
HAS-BLED (median [IQR])	1.0 [0.0, 1.0]	2.0 [2.0, 3.0]
HAS-BLED category (%)		
0	7844 (37.9)	453 (0.6)
1	9297 (45.0)	10659 (15.2)
2	3083 (14.9)	28087 (40.1)
3	400 (1.9)	24598 (35.1)
>3	49 (0.2)	6223 (8.9)
GARFIELD-AF stroke (median [IQR])	0.68 [0.52, 0.94]	1.33 [0.89, 2.09]
GARFIELD-AF, bleed (median [IQR])	0.59 [0.44, 0.76]	1.27 [0.95, 1.69]

Table S3 footnotes. Abbreviations. TIA; transient ischemic attack, SE; systemic embolism, OAC; oral anticoagulants, NOAC; non-vitamin-K antagonist, VKA; vitamin-K antagonist; NSAID; non-steroidal anti-inflammatory drug, ADP; adenosine diphosphate, PCI; Percutaneous coronary intervention, CABG; Coronary Artery Bypass Grafting.

Table S4. Logistic regression coefficients of GARFIELD-AF model for stroke/SE and major bleeding in the GARFIELD-AF Global cohort and the Danish AF cohort.

Variable	GARFIELD-AF Global registry	Danish AF cohort	P value*
Stroke/SE			
Age	0.030	0.026	<0.001
Prior Stroke/SE	0.952	1.572	<0.001
Bleeding	0.432	0.191	0.001
Heart failure	0.319	0.065	0.269
Chronic kidney disease	0.574	0.091	0.332
OAC	-0.582	-0.396	<0.001
Major bleeding			
Age	0.039	0.041	<0.001
Vascular disease	0.515	0.363	<0.001
Chronic kidney disease	0.577	0.865	<0.001

Table S4 footnotes. Abbreviations. SE; systemic embolism, OAC; oral anticoagulant.

* P value for coefficients in the Danish AF cohort

Figure S1. Flowchart of study population

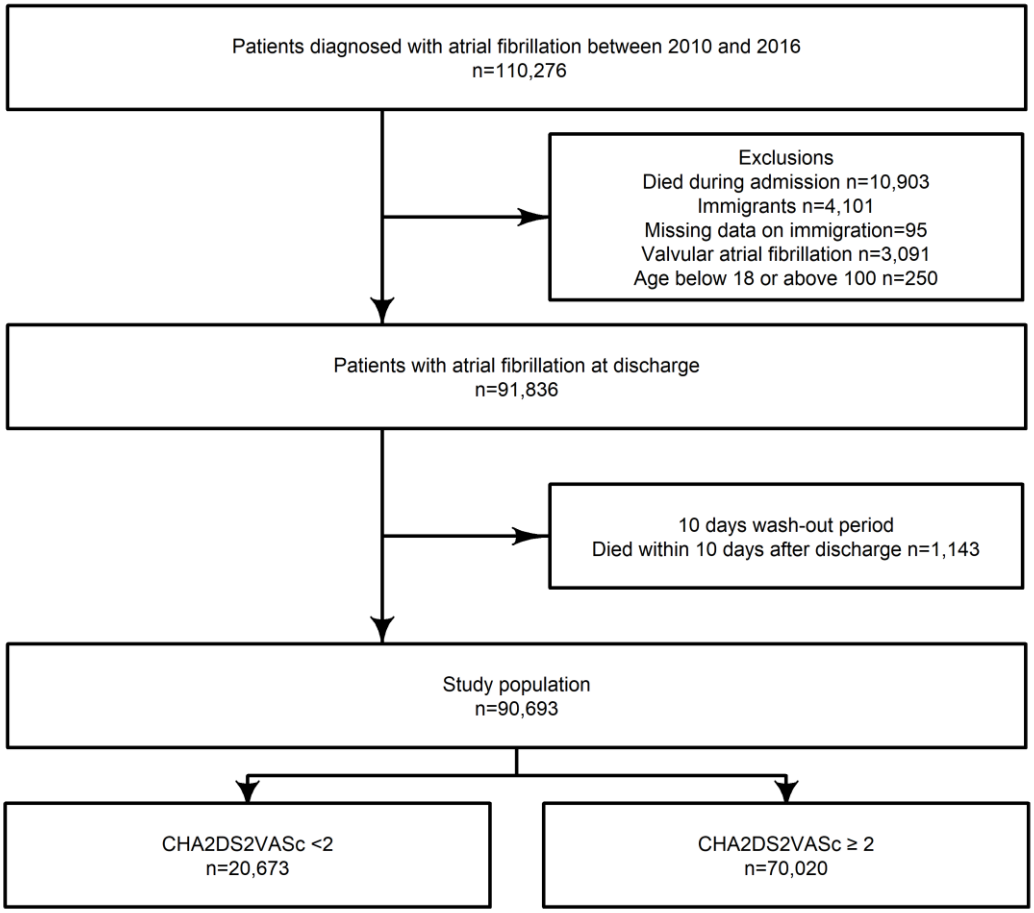

Figure S2. Cumulative incidence of ischemic stroke in the Danish population stratified by low and high stroke risk

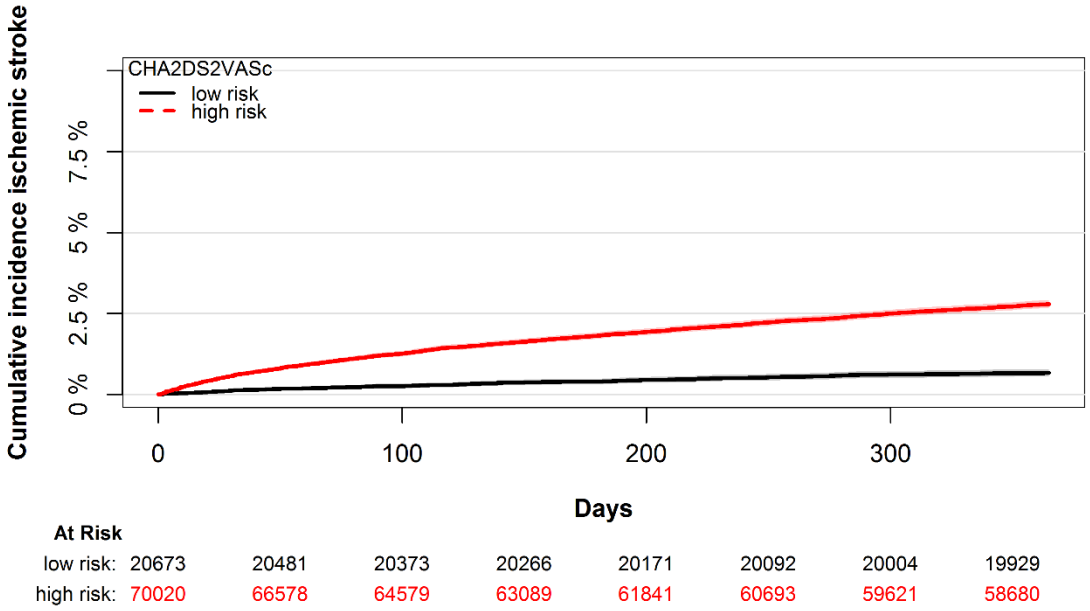

Figure S2 legend. Low risk patients were defined as CHA_2DS_2-VASc score (≤2 for women, 0-1 for men and >2 for women and >1 for men).

TRIPOD Checklist: Prediction Model Validation

Section/Topic	Item	Checklist Item	Page
Title and abstract			
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	2
Introduction			
Background and objectives	3a	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
	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	4
Methods			
Source of data	4a	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
	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	5
Participants	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	5
	5b	Describe eligibility criteria for participants.	5
	5c	Give details of treatments received, if relevant.	5-6
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	6
	6b	Report any actions to blind assessment of the outcome to be predicted.	6
Predictors	7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	6
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	6
Sample size	8	Explain how the study size was arrived at.	5-6
Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	5-6
Statistical analysis methods	10c	For validation, describe how the predictions were calculated.	7
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	7
	10e	Describe any model updating (e.g., recalibration) arising from the validation, if done.	7
Risk groups	11	Provide details on how risk groups were created, if done.	6-7
Development vs. validation	12	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	7
Results			
Participants	13a	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.	7-8
	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	7-8
	13c	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	7-9
Model performance	16	Report performance measures (with CIs) for the prediction model.	8-9
Model-updating	17	If done, report the results from any model updating (i.e., model specification, model performance).	8-9
Discussion			
Limitations	18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	11-12
Interpretation	19a	For validation, discuss the results with reference to performance in the development data, and any other validation data.	9-11
	19b	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	9-11
Implications	20	Discuss the potential clinical use of the model and implications for future research.	9-12
Other information			
Supplementary information	21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	NA
Funding	22	Give the source of funding and the role of the funders for the present study.	14

We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.

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GARFIELD-AF Model for Prediction of Stroke and Major Bleeding in Atrial Fibrillation: A Danish Nationwide Validation Study

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GARFIELD-AF Model for Prediction of Stroke and Major Bleeding in Atrial Fibrillation: A Danish Nationwide Validation Study

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Abstract

Objectives: To externally validate the accuracy of the GARFIELD-AF model against existing risk scores for stroke and major bleeding risk in patients with non-valvular atrial fibrillation (AF) in a population-based cohort.

Design: Retrospective cohort study.

Setting: Danish nationwide registries.

Participants: 90,693 patients with newly diagnosed non-valvular AF were included between 2010 and 2016, with follow-up censored at 1-year.

Primary and secondary outcome measures: External validation was performed using discrimination and calibration plots. C-statistics were compared with CHA_2DS_2VASc for ischemic stroke/systemic embolism (SE) and HAS-BLED for major bleeding/hemorrhagic stroke outcomes.

Results: Of the 90,693 included, 51,180 patients received oral anticoagulants (OAC). Overall median age (Q1, Q3) were 75 (66-83) years and 48,486 (53.5%) were male. At 1-year follow-up, a total of 2,094 (2.3%) strokes/SE, 2,642 (2.9%) major bleedings and 10,915 (12.0%) deaths occurred. The GARFIELD-AF model was well calibrated with the predicted risk for stroke/SE and major bleeding. The discriminatory value of GARFIELD-AF risk model was superior to CHA_2DS_2VASc for predicting stroke in the overall cohort (C-index:0.71,95%-confidence interval (CI):0.70-0.72 versus C-index:0.67,95%-CI:0.66-0.68, p<0.001) as well as in low-risk patients (C-index:0.64,95%-CI:0.59-0.69 versus C-index:0.57,95%-CI:0.53-0.61, p=0.007). The GARFIELD-AF model was comparable to HAS-BLED in predicting the risk of major bleeding in patients on OAC therapy (C-index:0.64,95%-CI:0.63-0.66 versus C-index:0.64,95%-CI: 0.63-0.65, p=0.60).

Conclusion: In a nationwide Danish cohort with non-valvular AF, the GARFIELD-AF model adequately predicted the risk of ischemic stroke/SE and major bleeding. Our external validation confirms that the

GARFIELD-AF model was superior to CHA_2DS_2VASc in predicting stroke/SE and comparable with HAS-BLED for predicting major bleeding.

Strengths and limitations of this study

- This validation study was able to compare prediction performance GARFIELD-AF model versus CHA_2DS_2VASc for stroke and HAS-BLED for major bleeding in patients with atrial fibrillation.
- This study used a large contemporary population-based cohort with atrial fibrillation with many events and very limited loss to follow-up.
- The validation was based on ICD-10 coding from the Danish registries which is prone to misclassification bias and lacked clinical measurements.

INTRODUCTION

Atrial fibrillation (AF) is a common cardiac arrhythmia with a lifetime prevalence of 20-30% and is the cause of one in four strokes. [1] AF is associated with an increased risk of several cardiovascular conditions, most notably a nearly 5-fold increased stroke risk. [2, 3] The risk of stroke can be substantially diminished by thrombotic prophylaxis. [4, 5] However, 20-40% of potentially eligible patients do not receiving oral anticoagulant (OAC) therapy. [6-8] The most important and modifiable contributing factor is inappropriate risk assessment, with underutilization of existing risk scores, resulting in overestimation of bleeding risks and underestimation of potential stroke risk. [9, 10] Recently, the Global Anticoagulant Registry in the FIELD –Atrial Fibrillation (GARFIELD-AF) model was developed that allowed for simultaneous calculation of death, stroke, and bleeding risks in an international prospective registry of patients with newly diagnosed AF. [11] In the GARFIELD-AF and ORBIT-AF registries, the GARFIELD-AF model was found to improve discrimination of the existing risk scores for stroke (CHA_2DS_2-VASc) and bleeding (HAS-BLED). [11-13] These registries may not cover the full spectrum of patients with AF, which warrants external validation of these risk scores in other population-based cohorts. We aimed to 1) externally validate the GARFIELD-AF model of ischemic stroke and major bleeding outcomes among patients with newly diagnosed AF in a large contemporary Danish cohort and 2) perform a head-to-head comparison of the predictive properties of GARFIELD-AF model with CHA_2DS_2-VASc for thromboembolic events and HAS-BLED for major bleeding. We did not externally validate the GARFIELD-AF model for risk of death, as we did not have blood pressure and heart rate measurements; covariates that the GARFIELD-AF model for death requires.

MATERIALS AND METHODS

We reported our findings according to the TRIPOD (Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis) criteria. [14]

Data sources

We used the Danish nationwide registers cross-linking The Civil Registration System, The Danish National Patient Register (DNPR), and The Danish Drug Statistical Registry. The Civil Registration

System holds data on age, sex, and vital status. DNPR contains all hospital admissions according to ICD-10 and procedures. The Danish Drug Statistical Registry was used to characterize pharmacotherapy in which all claimed drug prescriptions are registered. To compare characteristics (baseline and outcomes) of the Danish registry we used data from the GARFIELD-AF registry which, in brief, is an observational, multicentre, international study of newly diagnosed AF with ≥1 risk factor for stroke. [15]

Study population

From the DNPR, patients aged ≥18 years with a primary or secondary diagnosis of AF or atrial flutter (International Classification of Diseases, Tenth Revision [ICD-10]: I48), hospitalization or outpatient visit, were included from January 1, 2010 until August 1st 2016 with follow-up to August 1st 2017. The diagnosis of AF in the DNPR has a positive predictive value of 94.0%. [16] Patients with rheumatic valvular heart disease or valve interventions were excluded. To allow patients time to fill their prescriptions after discharge, a 10-day wash-out period was used. Due to no data on race/ethnicity in the The Civil Registration System, we excluded immigrants and those with missing information on immigration and presumed Caucasian/European-white for non-immigrants. Given complete nationwide coverage of DNPR missing data is not present. For baseline characteristic and outcome comparison, we included the worldwide enrolled GARFIELD-AF patients and the patients enrolled from the Scandinavian sites; Denmark, Sweden, Norway, Finland (GARFIELD-AF Scandinavia).

Covariates, GARFIELD-AF model, CHA_2DS_2-VASc, and HAS-BLED

For the Danish AF cohort, all baseline variables were defined from ICD-10 codes, as any primary or secondary diagnosis, inpatient or outpatient, registered up to 10 years prior to the inclusion date. Pharmacotherapy at baseline was identified by Anatomical Therapeutic Chemical (ATC) codes of prescription drugs claimed up to 180 days prior to the inclusion date. For oral anticoagulants, within the 180 days the latest prescription filled of either vitamin K antagonist (VKA) or non-vitamin K oral anticoagulants (NOAC) was used. Prescriptions claimed for anti-diabetic drugs were used as proxy for diabetes mellitus. Hypertension was defined as claimed prescription for a combination of at least two of the seven different antihypertensive drugs classes as previously reported. [17] The algorithm for GARFIELD-AF 1-year risk of ischemic stroke/systemic embolism (SE) relies on the following variables:

age (in years), history of ischemic stroke, prior bleeding (any recorded in medical records), heart failure (medical history of heart failure, or ejection fraction of <40%), chronic kidney disease (CKD) (stage III-V), race/ethnicity, and use of oral anticoagulant (VKA or NOAC). The algorithm for GARFIELD-AF 1-year risk of major bleeding/haemorrhagic stroke was developed in patients taking OAC and involves age, chronic kidney disease (CKD), and vascular disease, in which the latter is defined as history of myocardial infarction (MI) or unstable angina, aortic, or peripheral artery disease. The CHA_2DS_2-VASc score is composed of age, sex, a history of heart failure, hypertension, stroke, transient ischemic attack (TIA), thromboembolism, and/or diabetes. HAS-BLED is composed of age, uncontrolled hypertension, renal disease, liver disease, labile international normalized ratio (INR), medication use predisposing to bleeding, and a history of stroke, major bleeding and/or predisposition to bleeding. All covariates were based on ICD-10 codes. The equations for these respective scores and ICD-10 codes can be found in *Table S1*.

Definitions of end points

The primary efficacy endpoint for this study involved a 1-year composite of ischemic stroke or SE. The primary safety endpoint involved a composite of haemorrhagic stroke or major bleeding. Major bleeding was defined as an organ-specific bleeding requiring hospitalization. [18] A list of ICD-10 codes used to compute these definitions can be found in *Table S2.* In the GARFIELD–AF cohorts, the occurrence of 'major bleeding' was defined according to the International Society on Thrombosis and Haemostasis (ISTH) criteria. [11, 15, 19]

Patient and public involvement

Patients or the public were not involved in the design of the study

Statistical Analyses

For the Danish AF cohort, we stratified baseline characteristics by CHA_2DS_2-VASc score (≤2 for women, 0-1 for men and >2 for women and >1 for men). The Danish AF cohort were followed for a maximum of 1 year from the discharge date and until the event of interest (stroke/SE or major bleeding), death, emigration or end of follow-up (August, 2017). For all three cohorts (Danish AF cohort, GARFIELD Scandinavia, GARFIELD global), 1-year absolute risks of stroke/SE and major

bleeding were estimated non-parametrically using the Aalen-Johansen estimator with competing risk of death. For the Danish AF cohort, using a logistic regression model we used the original coefficients from the GARFIELD-AF model development study. The discriminative performance of GARFIELD-AF for predicting ischemic stroke/SE and major bleeding hospitalizations was assessed using receiver operating characteristics (ROC) curves and reported as area under the curve (AUC) values. The C-index with 95% confidence intervals (CI) was reported as a measure of discrimination. As there was no censoring issue because the data did not contain any loss to follow-up within the first year of the study period, the significance test of C-index differences was tested for significance with DeLongs method. [20] Calibration was assessed by calculating deciles of predicted probabilities and plotting the average predicting with the observed Kaplan-Meier rate and 95% CI within each decile. A subgroup analysis for stroke prediction was undertaken for low risk patients. As a sensitivity analysis, we estimated the logistic regression coefficients for each individual covariate used in the GARFIELD-AF models. Statistical analyses were performed using R software (Team RC. R: A Language and Environment for Statistical Computing. 2019).

RESULTS

From the Danish registries, a total of 110,276 patients were diagnosed with AF between 2010 and 2016. Of those patients, 91,836 met the inclusion criteria for the study (Figure S1). Of these, 70,020 were identified as high risk and 20,673 was identified as low risk of stroke/SE. A total of 51,180 were on OACs. From the GARFIELD-AF registries, 52,080 patients with AF were included globally, and 2,396 patients were included from the Scandinavian sites.

Characteristics of study participants

Baseline characteristics for all three cohorts (Danish AF cohort, GARFIELD Scandinavia, GARFIELD global) are shown on Table 1. Compared to GARFIELD Scandinavia, the Danish AF cohort had a more equal representation of men and women (54% vs 58%) and was older (median age 75 vs 73). There were also notable differences in comorbidities, in which diabetes, hypertension, and chronic kidney disease were less prevalent in the Danish AF cohort, whereas a history of bleeding (11.6% vs 1.9% vs. 2.5%) was much more prevalent compared with the GARFIELD Scandinavia or global cohorts. Despite these differences the median CHA_2DS_2Vasc scores were comparable among all

cohorts but the HAS-BLED median was higher in the Danish AF cohort. For the GARFIELD model, the median GARFIELD scores were higher in the Danish AF cohort than both GARFIELD cohorts. The use of OAC therapy was 56.4% in the Danish AF cohort, which was lower than the reported percentages in GARFIELD Scandinavia (68.0%) and GARFIELD global (60.8%). The use of aspirin, ADP-inhibitors and NSAIDs was higher in the Danish AF cohort. The characteristics of patients at low (CHA_2DS_2Vasc of 0-1 in men and 1-2 in women; n=20,673) and high risk (n=70,020) for the Danish AF population is displayed in Table S3. The median [IQR] for CHA_2DS_2-VASc and HAS-BLED scores in the high-risk group were 4 [3-5] and 2 [2-3].

Clinical outcomes at 1-year Follow-up

Table 2 displays the number of stroke/SE, major bleeding, and all-cause mortality for the Danish AF cohort and GARFIELD-AF cohorts. For the Danish AF cohort, over a 1-year follow-up period a total of 2,094 (2.3%) stroke/SE, 2,642 (2.9%) major bleedings were reported. Annual mortality rates were high with 10,915 deaths (12.0 per 100 person years). For the OAC treated patients there were 4,521 deaths (8.8 per 100 person years) and for low risk patients there were 623 deaths (3.0 per 100 person years). For the GARFIELD-AF Global the rates of events were lower for stroke/SE (1.2%), major bleeding (1.1%), and deaths (4.7%). Similar rates the GARFIELD-AF Scandinavia the proportion of events were lower for stroke/SE (1.0%), major bleeding (1.7%), and deaths (3.7%). The cumulative incidence for ischemic stroke to 1-year for low and high-risk patients are presented in Figure S2 for the Danish AF cohort. The cumulative incidence of stroke/systemic embolism and ischemic stroke for the Danish AF cohort, GARFIELD Scandinavia, and GARFIELD Global can be found in Figure 1.

External validation of GARFIELD-AF model

The C-index for the GARFIELD-AF model for 1-year stroke was 0.71 (95%-CI: 0.70-0.72) in the overall Danish AF cohort of 90.693 patients and 0.64 (95%-CI: 0.59-0.69) in low-risk patients not requiring OAC therapy (n=20,673). The C-index for the GARFIELD-AF model for 1-year major bleeding risk was 0.64 (95%-CI 0.63-0.66) in patients using OAC therapy. The GARFIELD-AF model for stroke/SE and major bleeding scores were both well calibrated in the Danish AF cohort (Figure 2 and 3). The individual covariates in the GARFIELD-AF model expressed a similar regression coefficient for most

covariates in the Danish cohort when compared with the original derivation GARFIELD-AF cohort (Table S4).

GARFIELD-AF model versus CHA_2DS_2-VASc score for predicting stroke/SE

The AUC curves for predicting stroke using the GARFIELD model and CHA_2DS_2-VASc scores are displayed in Figure 4A for the Danish AF cohort and Figure 4B for the low risk patients. The AUC and corresponding C-index for GARFIELD was significantly higher when compared with CHA_2DS_2Vasc for predicting stroke outcomes, in the overall cohort (C-index: 0.71, 95%-CI: 0.70-0.72 versus 0.67, 95%-CI: 0.66-0.68) as well as in low-risk patients (C-index: 0.62, 95%-CI: 0.59-0.69 versus 0.57, 95%-CI: 0.53-0.61).

GARFIELD-AF model versus HAS-BLED score for predicting major bleeding/haemorrhagic stroke

Figure 4C illustrates the AUC curves for the prediction of major bleeding based on the GARFIELD and HAS-BLED scores in patients taking OAC therapy. The discriminatory value of GARFIELD was comparable with HAS-BLED: C-index: 0.64 (95%-CI: 0.63-0.66) versus C-index: 0.64 (95%-CI: 0.63-0.65), respectively.

Table 3 displays available evidence comparing the discriminatory properties of various models for stroke/SE and major bleeding.

Discussion

In a large unselected contemporary Danish AF cohort, our study demonstrates that the GARFIELD-AF model serves as a reliable risk stratification tool. We found that the GARFIELD-AF model surpasses the widely used CHA_2DS_2-VASc score in predicting the risk of stroke, both in high and low-risk patients. For predicting major bleeding, the three-item GARFIELD-AF model is on par with HAS-BLED among anticoagulated patients with AF.

Risk-stratification of patients with AF is essential to mitigate the risk of stroke/SE when initiating anticoagulation therapy. As such, the easy-to-calculate CHA_2DS_2-VASc score serves as the risk-stratification tool recommended by international guidelines to commence therapy when the risk of

stroke reaches a threshold of >2% per annum. [21] Prior studies have shown that guideline-adherent (risk-stratified) anticoagulation therapy is associated with a 60-70% reduction in thromboembolic associated complications and mortality. [22] Despite these reductions in stroke risk, there is still room for improvement in risk stratification of patients with AF and anticoagulation therapy. In this regard, the GARFIELD-AF model, which calculates the risk of stroke, death, and major bleeding, is promising, particularly as it performed better than the CHA_2DS_2-VASc and HAS-BLED. [11] The GARFIELD-AF model is not categorized into risk groups but instead provides risk prediction on a continuous scale and provides risk estimates of the risk of stroke/SE and bleeding (and mortality when blood pressure and heart rate data are available) in a single calculation and based on routinely collected data would have potentially wide clinical applications.

Underuse of anticoagulation therapy is a well-known problem in particular in high-risk patients. [23] Our study found that 73.1% of patients with increased stroke risk (n=51,180, CHA_2DS_2-VASc>2 in women and >1 in men) received anticoagulation therapy. Studies suggests that treatment barriers are based on overestimation of bleeding risks (for example recurrent falls and prior peptic ulcers) and lack of reliable risk stratification tools and readily available information that does not rely on specific lab tests such as HAS-BLED. [9, 10, 23]

To provide predictions for bleeding risk, several bleeding scores have been developed, of which HAS-BLED has been most rigorously tested. [24, 25] While the HAS-BLED risk score is clinically useful to identify patients at high bleeding risk, it requires information that may not always be available in outpatient and primary care settings, such as information on liver function tests, INR status, and presence of anemia. This may be a limitation for the implementation of this score in low-resource settings and is of relevance as the majority (60%) of community-dwelling patients with AF are seen in primary care. [26, 27] Moreover, primary care physicians achieve lower anticoagulation rates compared with hospital-based physicians. [28, 29] While there are multiple reasons for these differences, which include differences in populations, with high percentage of (relative) contraindications (40-65%) and care-related factors, the lack of an integral decision tool impedes informed decisions on initiating or continuing antithrombotic therapy. [10, 30]

In the present study, the external validation show that GARFIELD-AF is well calibrated with the predicted risks, and the good calibration aligns well with the original GARFIELD-AF derivation

cohort. [11] GARFIELD-AF score has improved discriminatory abilities compared to CHA_2DS_2-VASc score in stroke prediction and on par with HAS-BLED for bleeding prediction. To our surprise, our external validation of GARFIELD-AF discriminatory c-index for stroke prediction was slightly higher (0.71) than the c-index in the original GARFIELD cohort (0.69). Furthermore, the Danish AF cohort were older with more stroke events than both GARFIELD cohorts and higher predicted risk than the GARFIELD cohorts. The opposite was the case for major bleeding prediction where the original GARFIELD cohort had better discriminatory abilities than HAS-BLED. The significant differences in the cohort characteristics, for example higher HAS-BLED and more use of combined OACs and antiplatelet therapy in the Danish AF cohort, and definitions of covariates and outcomes are likely to play a key role in both instances.

The value of CHA_2DS_2-VASc score in defining patients with a truly low risk of stroke is uncertain, partly because the number of patients to accurately assess lower risk patients in the original studies was insufficient. [12, 31] The evaluation of the performance of risk scores in this low-risk category is important, as it determines the threshold when initiating antithrombotic therapy outweighs the risk of bleeding. In our study although both models had modest predictive discrimination for low risk patients, we found that in these patients the GARFIELD-AF model was well calibrated and provided a better prediction than CHA_2DS_2-VASc score in indicating which patients are truly at low-risk for subsequent stroke.

Limitations and future directions

The primary limitation of this study is that definitions are based on administrative ICD-10 codes which are prone to non-systematic misclassification bias. Discrepancies exist between the GARFIELD-AF registry and the Danish registries in the definitions of comorbidities and clinical outcome data. This was most notable for major bleeding and stroke/SE events and CKD. In the Danish AF cohort, selected ICD-10 codes for bleeding hospitalizations were applied, whereas GARFIELD-AF applied the ISTH criteria for major bleeding, which are more restrictive. Apart from differences in disease definitions, the relative high number of bleeding and stroke/SE events in the Danish AF cohort could also be explained by site of enrollment (only hospital/outpatient). Similar data limitations apply to the construction of CHA_2DS_2-VASc score and HAS-BLED scores which was calculated from ICD-10 code usage although this study followed the standards set by other researchers using the same Danish

registries [17]. Specifically, we were unable to account for labile INR component of the HAS-BLED score. Another limitation was the inability to ascertain ethnicity status which is an integrated covariate of the GARFIELD-AF model. Therefore, we excluded immigrants to strengthen the assumption of European/Caucasian ethnicity in the cohort. The GARFIELD Scandinavian cohort consisted of 99.3% Caucasians. Population-based studies in other more ethnically diverse cohorts are warranted. We did not asses net reclassification improvement as this statistic is not appropriate when using it for point-based scores, such as CHA_2DS_2-VASc. [32] For the implementation of the GARFIELD-AF model, an online risk calculator already exists. A next step would be to provide an electronic health record integrated solution, in which stroke/SE and bleeding risks are automatically calculated when a patient is identified with AF. Doing so, would promote balanced and evidence-based decision making on anticoagulation therapy. Integrating the GARFIELD-AF model into electronic health records would also provide a way for anonymous monitoring of outcomes of patients in which the GARFIELD-AF model was applied, which can be used to further optimize risk prediction.

Conclusion

The GARFIELD-AF model adequately predicted the risk of ischemic stroke/SE and major bleeding/haemorrhagic stroke in a nationwide Danish cohort of contemporary patients with non-valvular AF. Our external validation confirms that the performance of the GARFIELD-AF model was superior to CHA_2DS_2VASc in predicting stroke/SE both in high-risk and in low risk patients and comparable with HAS-BLED for predicting major bleeding. The GARFIELD-AF model holds an advantage over the existing risk scores as it permits for simultaneous evaluation of death, stroke and bleeding risks and uses readily available clinical parameters. As such, the tool may lead to more informed treatment decisions, improve monitoring for bleeding complications, and improve outcomes for patients treated for AF in the community.

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Conflicts of interests:

KAAF: has received research grants Bayer/Janssen and AstraZeneca and Consulting/Fees Bayer, Sanofi/Regeneron and Verseon

FWAV: has received honoraria for consulting and presentations from Bayer HealthCare, Boehringer Ibgelheimy, BMSPfizer and Daiichi-Sankyo

GG: has ownership of stocks in Novo Nordisk Pharmaceuticals and reports research grants from Pfizer, Bristol Myers Squibb, Boehringer Ingelheim and Bayer.

CTP: declares grants for studies from Bayer.

Other authors have no conflicts of interest to declare

Patient consent:

Obtained

Ethics approval:

For the GARFIELD-AF registry an independent ethics committee and hospital-based institutional review board approvals were obtained for the registry protocol. In Denmark, retrospective register studies do not require approval from the ethics committees. The Danish Data Protection Agency approved this study (Ref no: 2007-58-0015, I-Suite nr: 02732, GEH-2014-014). Data were made available in an anonymized format such that specific individuals could not be identified.

Contributors:

FD, REH, MR, FWAV, KAAF, AKK, HVW and KP contributed to the study concept and design; FD, and KP conducted the data analysis; REH and FD and drafted the manuscript; FD, REH, MR, FWAV, KAAF, AKK, HVW JC, JLP, PVR, TBL, CTP, GG critically reviewed all drafts of the manuscript.

Data sharing statement:

Due to restrictions related to Danish law and protecting patient privacy, the combined set of data as used in this study can only be made available through a trusted third party, Statistics Denmark. This state organisation holds the data used for this study. Any request on data access should be addressed to Statistics Denmark https://www.dst.dk/en.aspx#

Table 1. Baseline characteristics of patients from the Danish AF cohort, GARFIELD-AF Scandinavia, and GARFIELD-AF Global registries

	Danish AF cohort	**GARFIELD-AF Scandinavia**	**GARFIELD-AF Global**
n	90693	2396	52080
Age (median [IQR])	75 [66.0, 83.0]	73.0 [66.0, 78.0]	71.0 [63.0, 78.0]
Sex, male (%)	48486 (53.5)	1389 (58.0)	29068 (55.8)
Race, Caucasian (%)	NA	1860 (99.3)	32028 (63.1)
Diabetes (%)	10900 (12.0)	387 (16.2)	11555 (22.2)
Stroke/TIA (%)	12827 (14.1)	325 (13.6)	3879 (7.5)
Systemic embolism (%)	448 (0.5)	6 (0.3)	335 (0.6)
History of bleeding (%)	10544 (11.6)	46 (1.9)	1318 (2.5)
Vascular disease (%)	15305 (16.9)	268 (11.2)	7682 (14.8)
Chronic kidney disease (%)	4224 (4.7)	185 (7.7)	5360 (10.3)
Heart Failure (%)	14961 (16.5)	348 (14.5)	11758 (22.6)
Ischemic heart disease (%)	13445 (14.8)	331 (13.8)	11265 (21.6)
Hypertension (%)	55665 (61.4)	1659 (69.4)	39643 (76.3)
VTE or PE (%)	5141 (5.7)	77 (3.2)	1355 (2.6)
NOAC (%)	23212 (25.6)	521 (21.7)	11004 (21.1)
VKA (%)	27968 (30.8)	1110 (46.3)	20708 (39.8)
OAC (%)	51180 (56.4)	1631 (68.0)	31712 (60.8)
VKA + AP (%)	10773 (11.9)	181 (7.6)	4827 (9.4)
NOAC + AP (%)	7608 (8.4)	47 (2.0)	1896 (3.7)
NSAID (%)	13078 (14.4)	23 (1.0)	1701 (3.3)
Acetylsalicylic acid (%)	32890 (36.3)	413 (17.2)	14636 (28.1)

ADP-inhibitor (%)	9128 (10.1)	89 (3.7)	3580 (6.9)
CABG (%)	3291 (3.6)	92 (3.9)	1625 (3.2)
CHA_2DS_2VASC (median [IQR])	3.0 [2.0, 4.0]	3.0 [2.0, 4.0]	3.0 [2.0, 4.0]
CHA_2DS_2VASC (%)			
0	5678 (6.3)	19 (0.8)	1516 (2.9)
1	10231 (11.3)	279 (11.7)	6369 (12.4)
2	16137 (17.8)	530 (22.2)	10230 (19.9)
3	20143 (22.2)	626 (26.2)	12138 (23.6)
4	19378 (21.4)	526 (22.1)	11022 (21.4)
5	11020 (12.2)	238 (10.0)	5895 (11.5)
>5	8106 (8.9)	167 (7.0)	4238 (8.2)
HAS-BLED (median [IQR])	2.0 [1.0, 3.0]	1.0 [1.0, 2.0]	1.0 [1.0, 2.0]
HAS-BLED category n, missing (%)		1088 (1308)	37549 (14531 - missing)
0	8297 (9.1)	169 (15.5)	5471 (14.6)
1	19956 (22.0)	507 (46.6)	16169 (43.1)
2	31170 (34.4)	301 (27.7)	11692 (31.1)
3	24998 (27.6)	87 (8.0)	3570 (9.5)
>3	6272 (6.9)	24 (2.2)	647 (1.7)
GARFIELD-AF model, stroke, median (IQR)	1.10 [0.75, 1.82]	0.80 [0.60, 1.10]	0.90 [0.70-1.40]
GARFIELD-AF model, bleed, median (IQR)	1.08 [0.74, 1.54]	0.90 [0.70,1.30]	1.00 [0.70-1.40]

Table 1 footnotes. Abbreviations: TIA; transient ischemic attack, SE; systemic embolism, OAC; oral anticoagulants, NOAC; non-vitamin-K antagonist, VKA; vitamin-K antagonist; AP; anti-platelet therapy, NSAID; non-steroidal anti-inflammatory drug, ADP; adenosine diphosphate, CABG; Coronary Artery Bypass Grafting.

Table 2. Number of events and deaths for one 1-year follow-up in the Danish population (all patients, patients on OAC, low risk patients), GARFIELD-AF Global, and GARFIELD-AF Scandinavia.

	Danish AF cohort (n=90693)	Patients treated with OAC (n=51180)	Low risk patients (n=20673)	GARFIELD Scandinavia (n=2396)	GARFIELD-AF Global (n=52080)
Ischemic Stroke/SE	2094	994	139	24	599
Major bleeding/Haemorrhagic stroke	2642	1492	242	28*	341
Deaths	10915	4521	623	88	2459

Table 2 footnotes. Low risk patients were defined as CHA_2DS_2-VASc score (≤2 for women, 0-1 for men and >2 for women and >1 for men). Abbreviations: OAC; oral anticoagulation. *Of those treated with OAC (n=1631), Of those treated with OAC (n=31712).

Table 3. Available evidence comparing the discriminatory properties of various models for stroke/SE and major bleeding [11, 24]

Outcome	Cohort	N	GARFIELD-AF - AUC (95% CI)	CHA_2DS_2-VASc /HAS-BLED - AUC (95% CI)
Stroke/SE	GARFIELD-AF	39,898	0.69 (0.67-0.71)	0.64 (0.61-0.66)
	ORBIT-AF	9,743	0.69 (0.64-0.75)	0.69 (0.64-0.74)
	Danish AF cohort	90,693	0.71 (0.70-0.72)	0.67 (0.66-0.68)
Stroke/SE low risk patients	GARFIELD-AF	7,882	0.65 (0.56-0.73)	0.59 (0.50-0.67)
	Danish AF cohort	20,673	0.64 (0.59-0.69)	0.57 (0.53-0.61)
Major bleeding	GARFIELD-AF	25,677	0.66 (0.62-0.69)	0.64 (0.61-0.68)
	ORBIT-AF	7,442	0.61 (0.58-0.64)	-
	SPORTIF III-V	3,550	0.56 (0.54-0.57)	0.58 (0.56-0.60)

	Danish AF cohort	51,180	0.64 (0.63-0.66)	0.64 (0.63-0.65)

Figure 1.

Figure 1 legend. Cumulative incidence of stroke/systemic embolism (panel A) and major bleeding (panel B) in the Danish AF cohort, GARFIELD-AF Scandinavia, and GARFIELD-AF Global.

Figure 2.

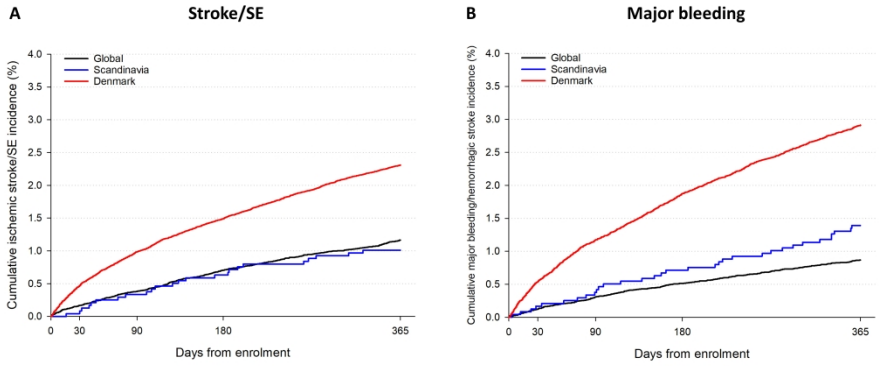
Figure 2 legend. Calibration plots of GARFIELD-AF model and stroke/SE risk in overall Danish population (A) and in low-risk patients (B). Predicted probability for GARFIELD (blackline), and actual observed cumulative incidence estimates with 95% CI for each GARFIELD score in deciles including a linear regression model (dashed line) and LOESS function of observed probability (red line).

Figure 3.

Figure 3 legend. Calibration plots of GARFIELD-AF model and major bleeding risk in Danish population. Predicted probability for GARFIELD (blackline), and actual observed cumulative incidence estimates with 95% CI for each GARFIELD score in deciles including a linear regression model (dashed line) and LOESS function of observed probability (red line).

Figure 4.

Figure 4 legend. Receiver Operating Characteristic curves of GARFIELD-AF model versus CHA_2DS_2VASc scores for predicting stroke in (A) the Danish AF cohort and (B) low-risk individuals and (C) GARFIELD-AF model versus HAS-BLED scores for predicting major bleeding in the Danish AF cohort in those receiving oral anticoagulants (n=51,180). Low risk stroke patients were defined as CHA_2DS_2-VASc score (≤2 for women, 0-1 for men and >2 for women and >1 for men).



Cumulative incidence of stroke/systemic embolism (panel A) and major bleeding (panel B) in the Danish AF cohort, GARFIELD-AF Scandinavia, and GARFIELD-AF Global.

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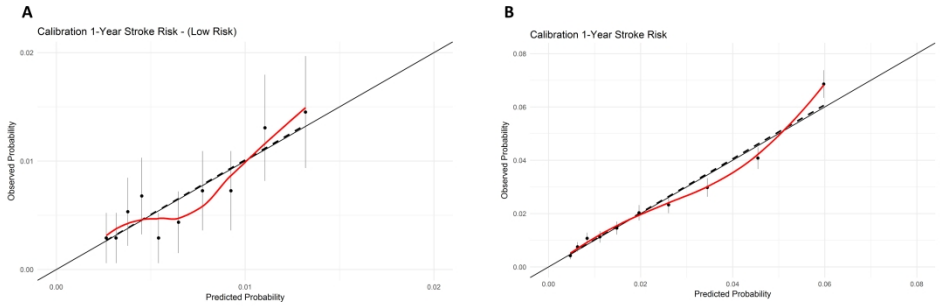
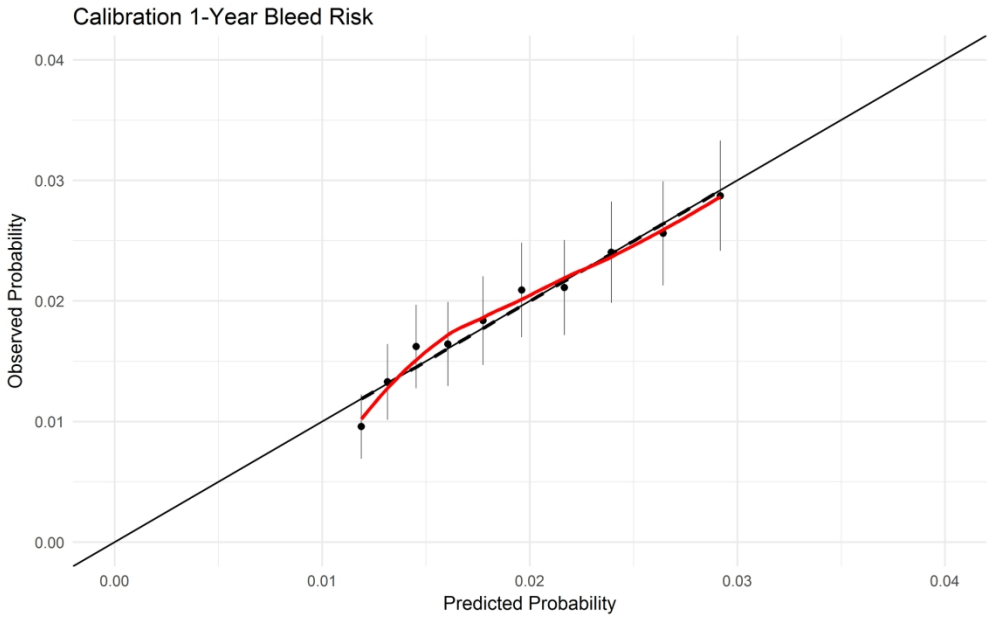


Calibration plots of GARFIELD-AF model and stroke/SE risk in overall Danish population (A) and in low-risk patients (B). Predicted probability for GARFIELD (blackline), and actual observed cumulative incidence estimates with 95% CI for each GARFIELD score in deciles including a linear regression model (dashed line) and LOESS function of observed probability (red line).

350x170mm (300 x 300 DPI)



Predicted probability for GARFIELD (blackline), and actual observed cumulative incidence estimates with 95% CI for each GARFIELD score in deciles including a linear regression model (dashed line) and LOESS function of observed probability (red line).

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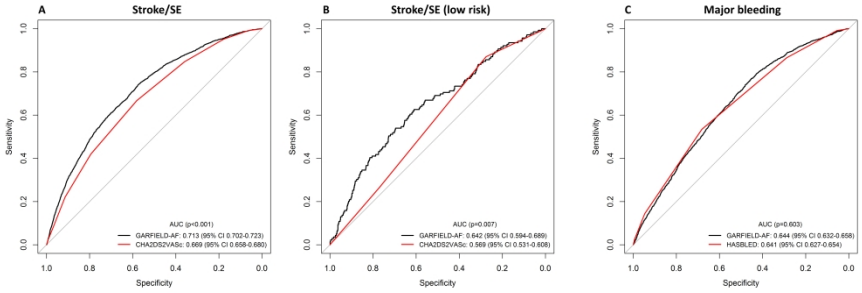

Receiver Operating Characteristic curves of GARFIELD-AF model versus CHA2DS2VASc scores for predicting stroke in (A) the Danish AF cohort and (B) low-risk individuals and (C) GARFIELD-AF model versus HAS-BLED scores for predicting major bleeding in the Danish AF cohort in those receiving oral anticoagulants (n=51,180). Low risk stroke patients were defined as CHA2DS2-VASc score (≤2 for women, 0-1 for men and >2 for women and >1 for men).

520x180mm (300 x 300 DPI)

SUPPLEMENTAL DATA FILE

Table S1. Equations of the risk scores

GARFIELD-AF stroke/SE (original)	100*(1-(0.991344397**(exp(0.0304823*(Age-60) + 0.952524717* stroke/TIA/SE + 0.432357326*Bleeding + 0.319129628* Heart failure + 0.574919171* Chronic kidney disease + 0.654249546*other region + 0.671380382*race- 0.582045773*OAC))))
GARFIELD-AF stroke/SE (modified for this analysis)	100*(1-(0.991344397**(exp(0.0304823*(Age-60) + 0.952524717* stroke/TIA/SE + 0.432357326*Bleeding + 0.319129628* Heart failure + 0.574919171* Chronic kidney disease - 0.582045773*OAC))))
GARFIELD-AF major bleeding	100*(1-(0.994488926**(exp(0.0389958*(AGE-60) + 0.515013074*vascular disease + 0.577378429* Chronic kidney disease))))
CHA_2DS_2-VASc	65≤ age <75: 1 point Age ≥75: 2 point Female sex: 1 point Heart failure: 1 point Hypertension: 1 point Ischemic stroke / TCI / Systemic embolism and thrombosis: 2 points Ischemic Heart Disease or Peripheral atherosclerosis: 1 point Diabetes: 1 point
HAS-BLED	Age >65: 1 point Hypertension: 1 point Chronic kidney disease: 1 point Liver disease: 1 point Ischemic stroke / TCI / Systemic embolism and thrombosis: 1

	points Bleeding: 1 point ASA or ADP inhibitors or Dipyridamole or NSAID: 1 point Alcohol: 1 point

Table S2. Definitions of covariates.

	ICD-10 codes
Atrial Fibrillation	I48
Non-Valvular Atrial Fibrillation	Presence of: I48 With absence of: Rheumatic heart valve disease, prostatic heart valve
Rheumatic heart valve disease	ICD10: Z952, Z954, I05, I06, I080A, I081A, I082A, I083A
Prostatic heart valve	KFKD, KFKH, KFMD, KFMH, KFGE, KFJF
Stroke / TIA / Systemic embolism and thrombosis (without hemorrhagic stroke), baseline	Ischemic: I63, I64 TIA: G458, G459 Systemic embolism and thrombosis: I74
Stroke/SE, endpoint	Ischemic: I63, I64 Systemic embolism and thrombosis: I74
Hospitalization for any bleeding, baseline	Heart: I312 Urine: N02, R31 Airways: R04 Eye: H313, H356, H431, H450, H052A Gastrointestinal: K228F, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K290, K298A, K625, K638B, K638C, K838F, K868G, K920, K921, K922, I850, I864A Intra-dural bleeds not hemorrhagic stroke: S064, S065, S066 Hemorrhagic stroke: I60, I61, I62, I690, I691, I692 Retro-peritoneal: K661 Thorax: J942 Anemia due to bleeding: D500, D62
Major bleeding (with hemorrhagic stroke)	Heart: I312 Urine; N02, R31 Eye: H313, H356, H431, H450 Airways: R04 Gastrointestinal: K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K280, K282, K284, K286, K920, K921, K922 Intra-dural bleeds not hemorrhagic stroke: S064, S065, S066, I692 Hemorrhagic stroke: I60, I61, I62, I690, I691 Thorax: J942 Retro-peritoneal: K661

	Anemia due to bleeding: D62
Heart Failure	Cardiomyopathy: I42 Heart failure: I50, I110 Lung edema: J81
IHD	Ischemic Heart Disease: I20-I25 • Angina pectoris: I20 • Acute myocardial infarction: I21, I22 • Complications to AMI: I23, • Other forms of ischemic heart disease: I24, I25
Peripheral artery disease	I70
Vascular disease	Presence of Ischemic heart disease or peripheral artery disease
Chronic Kidney Disease	N02, N03, N04, N05, N06, N07, N08, N11, N12, N14, N18, N19, N26, N158, N159, N160, N162, N163, N164, N168 Q61, E102, E112, E132, E142, I120, M321B
Pulmonary embolism	I26
Alcohol	F10, K70, E52, T51, K860, E244, G312, I426, O354, Z714, Z721, G621, G721, K292, L278A
Liver disease	B15, B16, B17, B18, B19, C22, K70, K71, K72, K73, K74, K75, K76, K77, Z944, I982, D684C
Diabetes Mellitus	Insulin: A10A Non-Insulin: A10B
OAC	VKA: Warfarin: B01AA03, Phenprocoumon: B01AA04 NOAC: Dabigatran: B01AE07, Rivaroxaban: B01AF01, Apixaban: B01AF02
Acetylsalicylic acid	B01AC06, N02BA01
ADP-inhibitors	B01AC04, B01AC24, B10AC22
NSAID	M01A without M01AX05
Hypertension as usage of combination of at least two of the seven different drugs classes at the same time.	1. Non-Loop: Thiazides C02L, C02DA, C07B, C07D, C09XA52, C03A, C03EA; Low-ceiling diuretics (excl. thiazides): C03B, C03X, C07C, C08G, C09BA, C09DA; Potassium-sparing agents (spiron): C03D, C03E,C03EB 2. Loop: High-ceiling diuretics (Loop) C03C,C03EB 3. Antiadrenergic agents: C02A, C02B, C02C

	4. Beta-blockers: C07A, C07B, C07C, C07D, C07F 5. Vasodilators: C02DB, C02DD, C02DG 6. Calcium channel blockers: C08, C09BB, C09DB 7. RASi: C09AA, C09BA, C09BB, C09CA, C09DA, C09DB, C09XA02, C09XA52

Table S3. Baseline characteristics for the Danish population, stratified by CHA_2DS_2VASC score. Low (0-1 men, 1-2 women) risk and high-risk.

	Low risk	High risk
n	20,673	70,020
age (median [IQR])	61 [54, 68]	78 [71, 85]
Sex, male (%)	13083 (63.3)	35403 (50.6)
Diabetes (%)	286 (1.4)	10614 (15.2)
Stroke/TIA (%)	0 (0.0)	12827 (18.3)
Systemic embolism (%)	0 (0.0)	448 (0.6)
History of bleeding (%)	1154 (5.6)	9176 (13.1)
Chronic kidney disease (%)	296 (1.4)	3928 (5.6)
Heart failure (%)	225 (1.1)	14736 (21.0)
Ischemic heart disease (%)	492 (2.4)	12953 (18.5)
OAC (%)	8801 (42.6)	42379 (60.5)
NOAC (%)	4307 (20.8)	18905 (27.0)
VKA (%)	4494 (21.7)	23474 (33.5)
venous thromboemobolism (%)	380 (1.8)	2301 (3.3)
Pulmonary embolism (%)	0 (0.0)	2460 (3.5)
Dipyridamole (%)	78 (0.4)	2629 (3.8)
Hypertension (%)	3601 (17.4)	52064 (74.4)
NSAID (%)	3113 (15.1)	9965 (14.2)
Acetylsalicylic acid (%)	3685 (17.8)	29205 (41.7)
ADP-inhibitor (%)	335 (1.6)	8793 (12.6)
PCI (%)	252 (1.2)	6104 (8.7)
CABG (%)	109 (0.5)	3182 (4.5)
CHA_2DS_2VASC (median [IQR])	1.0 [0.0, 1.0]	4.0 [3.0, 5.0]
CHA_2DS_2VASC (%)		
0	5678 (27.5)	-

1	10231 (49.5)	-
2	4764 (23.0)	11373 (16.2)
3	-	20143 (28.8)
4	-	19378 (27.7)
5	-	11020 (15.7)
>5	-	8106 (11.6)
HAS-BLED (median [IQR])	1.0 [0.0, 1.0]	2.0 [2.0, 3.0]
HAS-BLED category (%)		
0	7844 (37.9)	453 (0.6)
1	9297 (45.0)	10659 (15.2)
2	3083 (14.9)	28087 (40.1)
3	400 (1.9)	24598 (35.1)
>3	49 (0.2)	6223 (8.9)
GARFIELD-AF stroke (median [IQR])	0.68 [0.52, 0.94]	1.33 [0.89, 2.09]
GARFIELD-AF, bleed (median [IQR])	0.59 [0.44, 0.76]	1.27 [0.95, 1.69]

Table S3 footnotes. Abbreviations. TIA; transient ischemic attack, SE; systemic embolism, OAC; oral anticoagulants, NOAC; non-vitamin-K antagonist, VKA; vitamin-K antagonist; NSAID; non-steroidal anti-inflammatory drug, ADP; adenosine diphosphate, PCI; Percutaneous coronary intervention, CABG; Coronary Artery Bypass Grafting.

Table S4. Logistic regression coefficients of GARFIELD-AF model for stroke/SE and major bleeding in the GARFIELD-AF Global cohort and the Danish AF cohort.

Variable	GARFIELD-AF Global registry	Danish AF cohort	P value*
Stroke/SE			
Age	0.030	0.026	<0.001
Prior Stroke/SE	0.952	1.572	<0.001
Bleeding	0.432	0.191	0.001
Heart failure	0.319	0.065	0.269
Chronic kidney disease	0.574	0.091	0.332
OAC	-0.582	-0.396	<0.001
Major bleeding			
Age	0.039	0.041	<0.001
Vascular disease	0.515	0.363	<0.001
Chronic kidney disease	0.577	0.865	<0.001

Table S4 footnotes. Abbreviations. SE; systemic embolism, OAC; oral anticoagulant.

* P value for coefficients in the Danish AF cohort

Figure S1. Flowchart of study population

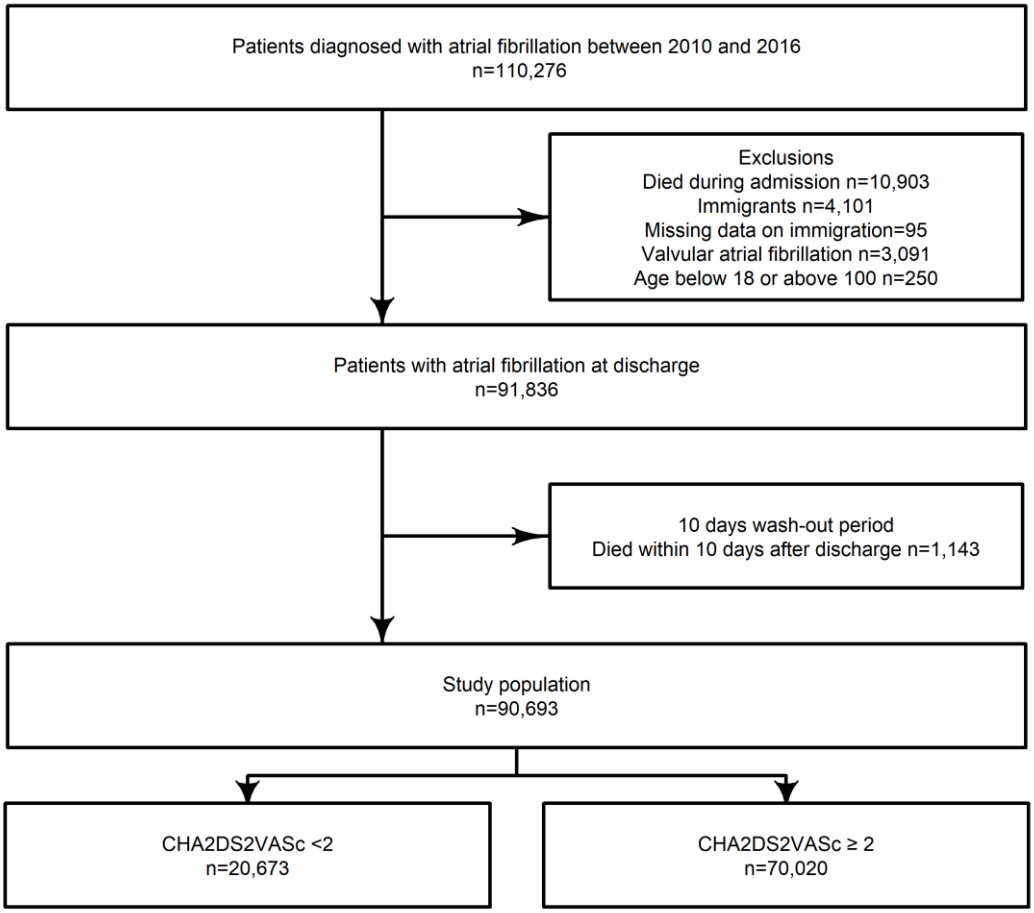

Figure S2. Cumulative incidence of ischemic stroke in the Danish population stratified by low and high stroke risk

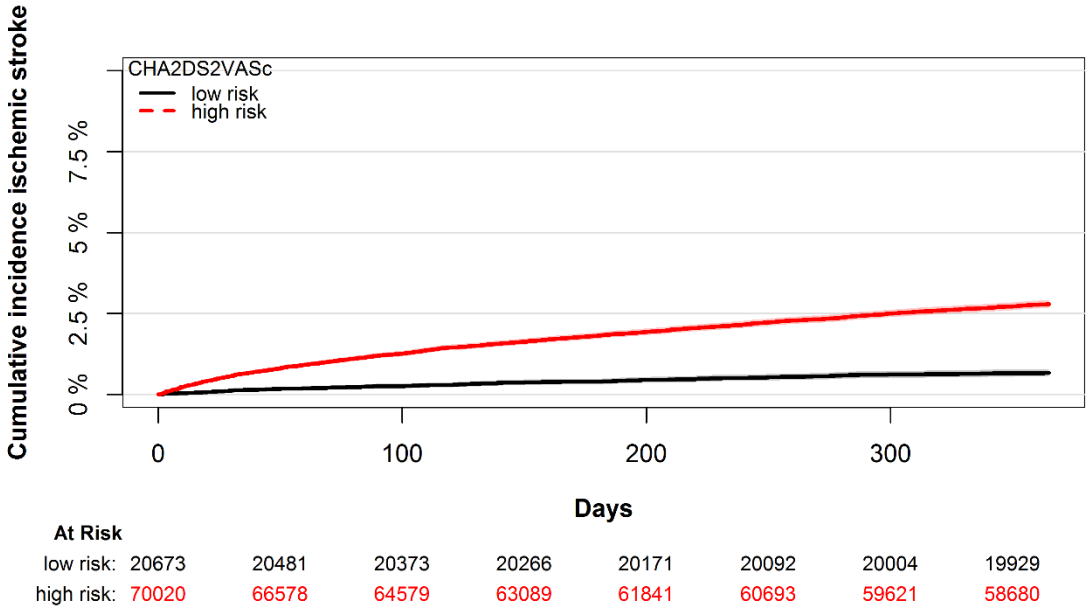

Figure S2 legend. Low risk patients were defined as CHA_2DS_2-VASc score (≤2 for women, 0-1 for men and >2 for women and >1 for men).

TRIPOD Checklist: Prediction Model Validation

Section/Topic	Item	Checklist Item	Page
Title and abstract			
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	2
Introduction			
Background and objectives	3a	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
	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	4
Methods			
Source of data	4a	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
	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	5
Participants	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	5
	5b	Describe eligibility criteria for participants.	5
	5c	Give details of treatments received, if relevant.	5-6
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	6
	6b	Report any actions to blind assessment of the outcome to be predicted.	6
Predictors	7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	6
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	6
Sample size	8	Explain how the study size was arrived at.	5-6
Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	5-6
Statistical analysis methods	10c	For validation, describe how the predictions were calculated.	7
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	7
	10e	Describe any model updating (e.g., recalibration) arising from the validation, if done.	7
Risk groups	11	Provide details on how risk groups were created, if done.	6-7
Development vs. validation	12	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	7
Results			
Participants	13a	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.	7-8
	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	7-8
	13c	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	7-9
Model performance	16	Report performance measures (with CIs) for the prediction model.	8-9
Model-updating	17	If done, report the results from any model updating (i.e., model specification, model performance).	8-9
Discussion			
Limitations	18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	11-12
Interpretation	19a	For validation, discuss the results with reference to performance in the development data, and any other validation data.	9-11
	19b	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	9-11
Implications	20	Discuss the potential clinical use of the model and implications for future research.	9-12
Other information			
Supplementary information	21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	NA
Funding	22	Give the source of funding and the role of the funders for the present study.	14

We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.