Title page

GARFIELD-AF risk score for mortality, stroke and bleeding within 2 years in patients with atrial fibrillation

Keith AA Fox[1], Saverio Virdone[2], Karen S Pieper[2], Jean-Pierre Bassand[2,3], A John Camm[4], David A Fitzmaurice[5], Samuel Z Goldhaber[6], Shinya Goto[7], Sylvia Haas[8], Gloria Kayani[2], Ali Oto[9], Frank Misselwitz[10], Jonathan P Piccini[11], Frederik Dalgaard[12], Alexander GG Turpie[13], Freek WA Verheugt[14] and Ajay K Kakkar[2,15], for the GARFIELD-AF Investigators

1 Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, UK

2 Thrombosis Research Institute (TRI), London, UK

3 Department of Cardiology, University of Besançon, Besançon, France

4 Cardiology Clinical Academic Group Molecular & Clinical Sciences Research Institute, St George's University of London, London, UK

5 Warwick Medical School, University of Warwick, Coventry, UK

6 Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

7 Department of Medicine (Cardiology), Tokai School of medicine, Kanagawa, Japan

8 Department of Medicine, Formerly Technical University of Munich, Munich, Germany

9 Department of Cardiology, Memorial Ankara Hospital, Ankara, Turkey

10 Formerly, Bayer AG, Berlin, Germany

11 Duke Clinical Research Institute, Durham, North Carolina, USA

12 Department of Cardiology, Hertlev & Gentofte Hospital, Hellerup, Copenhagen, Denmark

13 Department of Medicine, McMaster University, Hamilton, Canada

14 Department of Cardiology, Onze Lieve Vrouwe Gasthuis (OLVG), Amsterdam, The Netherlands

15 University College London, London, UK

*A complete list of investigators is given in the Supplementary file

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier for GARFIELD-AF: NCT01090362, ORBIT-AF I: NCT01165710; ORBIT-AF II: NCT01701817.

Contact information for corresponding author:

Keith AA Fox, FRCP, FESC, FMedSci, Professor of Cardiology, BHF Centre for Cardiovascular Science, University of Edinburgh, Queen's Medical Research Institute, 47 Little France Crescent, Edinburgh EH16 4TJ.

Email: k.a.a.fox@ed.ac.uk;

Tel: +44 131 242 6378

Short title: The integrated GARFIELD-AF risk tool

Word count for Abstract: 248 (250 max)
Word count for Manuscript: 4070
Number of figures: 4
Number of tables: 4
Number of references: 27
Number of supplementary files: 2

ABSTRACT

Aims

To determine whether the GARFIELD-AF integrated risk tool predicts mortality, non-haemorrhagic stroke/systemic embolism (SE), and major bleeding for up to two years after new onset AF and to assess how this risk tool performs compared with CHA_2DS_2-VASc and HAS-BLED.

Methods and results

Potential predictors of events included demographic and clinical characteristics, choice of treatment, and lifestyle factors. A Cox proportional hazards model was identified for each outcome by least absolute shrinkage and selection operator (LASSO) methods. Indices were evaluated in comparison with CHA_2DS_2-VASc and HAS-BLED risk predictors. Models were validated internally and externally in ORBIT-AF and Danish nationwide registries. Among the 52,080 patients enrolled in GARFIELD-AF, 52,032 had follow-up data. The GARFIELD-AF risk tool outperformed CHA_2DS_2-VASc for all-cause mortality in all cohorts. The GARFIELD-AF risk score was superior to CHA_2DS_2-VASc for non-haemorrhagic stroke, and it outperformed HAS-BLED for major bleeding in internal validation and in Danish AF cohort. In very low to low risk patients (CHA_2DS_2-VASc 0 or 1 (men) and 1 or 2 (women)), the GARFIELD-AF risk score offered strong discriminatory value for all the endpoints when compared to CHA_2DS_2-VASc and HAS-BLED. The GARFIELD-AF tool also included the effect of OAC therapy, thus allowing clinicians to compare the expected outcome of different anticoagulant treatment decisions (i.e., No OAC, NOACs or VKAs).

Conclusions

The GARFIELD-AF risk tool outperformed CHA_2DS_2-VASc at predicting death and non-haemorrhagic stroke, and it outperformed HAS-BLED for major bleeding in overall as well as in very low to low risk group patients with AF.

Keywords: GARFIELD-AF, CHA_2DS_2-VASc, risk stratification, atrial fibrillation

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with a nearly five-fold increased risk of stroke and two-fold increased risk of death (1, 2). The 2020 ESC guidelines for the diagnosis and management of AF suggest using the CHA_2DS_2-VASc risk score to identify patients at low risk (CHA_2DS_2-VASc score = 0 in men, or 1 in women) for whom antithrombotic therapy should not be prescribed. Oral anticoagulation (OACs) should be prescribed for stroke prevention in patients with CHA_2DS_2-VASc score ≥2 in men, or ≥3 in women and should considered in patients with a CHA_2DS_2-VASc score of 1 in men, or 2 in women. HAS-BLED is recommended to identify patients at high risk of bleeding. Non-VKA oral anticoagulants (NOACs) are recommended in preference to oral vitamin K antagonists (VKAs) except in patients with rheumatic mitral valve disease and/or an artificial heart valve (3).

We previously developed a Global Anticoagulant Registry in the FIELD–Atrial Fibrillation (GARFIELD-AF) risk model to predict all-cause mortality, stroke, and bleeding risks in patients with newly diagnosed AF. The early evaluation indicated that this was superior to existing risk scores for stroke (CHA_2DS_2-VASc) and bleeding (HAS-BLED) (4). The nationwide Danish AF cohort provides external validation and indicates that the GARFIELD-AF model is superior to CHA_2DS_2-VASc in predicting stroke/SE and is comparable with HAS-BLED for predicting major bleeding (5). Integrated clinical scores like GARFIELD-AF and other scores which incorporate biomarker measurement (6) demonstrate statistically significant though numerically modest improvement in the prediction of stroke risk when compared to CHA_2DS_2-VASc (3).

In this report, we aimed (1) to derive and validate a new risk model for predicting mortality, non-haemorrhagic stroke/SE and major bleeding up to two years after enrolment based on treatment selection. (2) To include the feature of treatment selection in GARFIELD-AF risk calculator to assist clinicians in applying guideline adherence to anticoagulation decisions for patients with AF.

MATERIALS AND METHODS

Registry population

The analysis was conducted in 52,080 patients enrolled in GARFIELD-AF between March 2010 and July 2016. The data were extracted from the study database on 19 November 2018. To minimize recruitment bias in GARFIELD-AF, investigator sites were selected randomly from representative care settings in each participating country (apart from 18 sites, out of >1000) and consecutive patients were enrolled, regardless of whether or not they received antithrombotic treatment. Eligible patients comprised adults (aged ≥18 years) who had been newly diagnosed with AF (not related to mechanical valves or severe valve disease), within the previous 6 weeks and had at least one unspecified risk factor for stroke as judged by the investigator.

Study procedures and outcome measures

The methods employed in GARFIELD-AF have been published (7, 8). In brief, baseline characteristics included: patient characteristics, medical history, care settings, type of AF, date and method of diagnosis, symptoms of AF, type of anticoagulant treatment (VKAs, factor Xa inhibitors [FXas] and direct thrombin inhibitors [DTIs], as well as antiplatelet treatment [AP]).

Data on components of the CHA_2DS_2-VASc (9) and HAS-BLED (10) risk stratification schemes were also collected to assess the risks of non-haemorrhagic stroke and major bleeding. Collection of follow-up data occurred at 4-monthly intervals based on telephone interviews and hospital records up to 24 months. The incidence of ischaemic stroke, transient ischaemic attack (TIA), systemic embolism (SE), acute coronary syndrome (ACS), hospitalisation, death (cardiovascular and non-cardiovascular), Congestive heart failure (CHF) (occurrence or worsening), and bleeding (severity and location) was documented. An audit and quality control programme was applied (11), and data were examined for completeness and accuracy by the coordinating centre (TRI, London, UK). By design, 20% of all electronic case report forms (eCRFs) in the GARFIELD-AF registry were monitored against source documentation at sites over the recruitment period and follow-up. Loss to follow-up was found to be 4.2% of all prospectively enrolled patients. Any events that occurred after two years follow-up were censored at two years. Patients with unavailable follow-up information were excluded from all the analyses.

Risk tool Design

The new risk stratification tool was derived from prospective data from the GARFIELD-AF registry. Models were trained on indicators for three events (all-cause mortality, non-haemorrhagic stroke/systemic embolism, and any major bleed) that occurred within 2 years of enrolment. As with the previous GARFIELD-AF risk models, the derivation of the GARFIELD-AF risk models followed the TRIPOD process for the development of predictive models (4, 12).

Comparisons of the performance of the new GARFIELD-AF risk models were made with (*a*) CHA_2DS_2-VASc score (for all-cause mortality, non-haemorrhagic stroke/SE), and (*b*) HAS-

BLED score for major bleeding. The performance of the new risk tool was tested in the whole GARFIELD-AF population as well as in patients treated and untreated with OACs for stroke prevention at baseline.

We also tested our hypothesis that the performance of the GARFIELD-AF risk model would be superior to the CHA_2DS_2-VASc score in discriminating patients with a low stroke risk. We considered a CHA_2DS_2-VASc score of 0 or 1 (men) and 1 or 2 (women) who may not benefit from anticoagulation (as defined by the ESC Guidelines) as representative of "very low to low" risk. As a sensitivity analysis, we also evaluated those with a CHA_2DS_2-VASc score of 0-2 (men) and 1-3 (women).

The validity of the GARFIELD-AF risk models was tested externally in patients with AF from an independent US-based registry, the ORBIT-AF registry as well as the Danish nationwide registries (5, 13-16).

Definitions

Non-haemorrhagic stroke/SE was defined as the combined end points of: ischaemic stroke, unknown-type stroke, systemic embolism and TIA. Major bleed was classified by investigators according to the International Society on Thrombosis and Haemostasis (ISTH) definition (17). Major bleeds, including intracranial bleeds, were defined as a combined end point of haemorrhagic stroke and any major bleed. Minor/non-major clinically relevant (NMCR) bleeds that required transfusion or that occurred in a critical site were reclassified as major bleeds.

Vascular disease included patients with peripheral artery disease or coronary artery disease (CAD). Hypertension was defined as a documented history of hypertension. Chronic kidney disease (CKD) was classified by investigators according to the National Kidney Foundation

Kidney Disease Outcomes Quality Initiative (NKF KDOQI) guidelines into two groups(18) moderate-to-severe, or mild or none. Congestive heart failure (CHF) was defined as current/prior history of congestive heart failure or left ventricular ejection fraction of <40%. Standard clinical definitions of stroke and TIA were used (19). ACS included unstable angina, STEMI, and non-STEMI.

The CHA_2DS_2-VASc score was the sum of points after addition of one point each for CHF, hypertension, diabetes, vascular disease, age 65-74 years, and female gender, and two points each for age ≥75 years and previous ischaemic stroke and systemic embolism (9). The HAS-BLED score was the sum of points after addition of one point each for uncontrolled hypertension (systolic blood pressure >160mmHg), moderate to severe CKD, cirrhosis, stroke history, bleeding history, elderly [>65] and heavy alcohol use (10) (fluctuations in international normalised ratios were not included in this study).

Ethics statement

Independent ethics committee and hospital-based institutional review board approvals were obtained, as necessary, for the registry protocol. Additional approvals were obtained from individual study sites. The registry is being conducted in accordance with the principles of the Declaration of Helsinki, local regulatory requirements, and the International Conference on Harmonisation Good Pharmacoepidemiological and Clinical Practice Guidelines. Written informed consent was obtained from all study participants. Confidentiality and anonymity of all enrolled patients are maintained.

Statistical modelling

Predictors of mortality, non-haemorrhagic stroke/SE, and major bleeding were identified using the least absolute shrinkage and selection operator (LASSO) regression. The predictors were selected from the list of potential predictors (Supplement List 1).

A Cox model was fitted with the selected parameters. Thirty-fold cross-validation was applied during the modelling process. Both a Kolmogorov-type supremum statistical test and a graphical examination of the Schoenfeld residuals were used to assess the Cox model proportional hazards assumption. All continuous covariates were tested for linearity and appropriate transformations were applied as needed. One imputed dataset was used for the model generation. The final model was established with multiple imputation. Combined hazard ratio estimates with 95% CI from five imputations were presented.

The equations using the base hazard and coefficients provide predicted probabilities for each outcome. These same equations are used in an online risk tool which provides an easy method for inputting the patient values.

Follow-up was censored at 2 years for those patients who were followed for a longer period. Comparison of the GARFIELD-AF risk model with existing scores (CHA_2DS_2-VASc, HAS-BLED) was performed displaying the c-index with 95% CI for a measure of discrimination. Calibration curves were used to show how well the predicted values were calibrated to the observed rates.

External validation

We evaluated the performance of the GARFIELD-AF risk model in two external populations: the ORBIT-AF registry (ORBIT-AF I and ORBIT-AF II) (13, 20) and the Danish nationwide registries including patients with AF (Danish AF cohort) (5).

ORBIT- AF Registry

Each score was recreated according to the definitions given in the original GARFIELD-AF study, using baseline values from the first study visit in each registry. From the list of variables in the simplified model, only history of bleeding and of carotid occlusive disease were unavailable in ORBIT-AF. In GARFIELD-AF, history of any bleeding was considered (independent of severity or site). In ORBIT-AF, history of gastrointestinal bleeding (GI) was substituted for history of bleeding. For the purpose of this validation, we considered that none of ORBIT-AF patients had carotid occlusive disease.

Danish AF Cohort

From the Danish Nationwide Patient Registry, patients aged ≥18 years with a primary or secondary diagnosis of AF or atrial flutter (International Classification of Diseases, Tenth Revision [ICD- 10]: I48), hospitalisation or outpatient visit, were included from January 1, 2010 until August 1st, 2015 with follow-up to August 1st 2017. 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. International Classification of Diseases, Tenth Revision (ICD-10) codes and Anatomical Therapeutic Chemical (ATC) codes were used as described in the previous publication (5). Additional codes were used for Carotid occlusion (DI625), diabetes (ICD-10, E10, E11, ATC-codes: A101A, A10B), and dementia (ICD-10: F00, F02, F01, F039, G30, ATC-code: N06D). For unavailable variables

like blood pressure, BMI, pulse, and smoking, the mean values from the GARFIELD-AF patients enrolled from Denmark, Sweden, Norway and Finland were used. The information on ethnicity was not available. Thus, for the purpose of the validation, all patients with a status of immigrant were excluded, and race was considered to be Caucasian for the remaining patients.

RESULTS

Baseline characteristics

Of 52,080 patients enrolled, 52,032 (99.9%) had available follow-up data. Table 1 provides the baseline characteristics for the patients and for the outcomes occurred within 2 years of follow-up. At baseline, the median (IQR) age was 71.0 (63.0 to 78.0) years, and 44.2% of patients were females. Overall, 66.8% of patients were prescribed AC therapy (39.3% VKAs and 27.5% NOACs, with or without APs), 21% received AP monotherapy, and 12.2% received no AC or AP therapy.

Clinical Outcomes

At 2 years, 3702 patients had died (event rate, 3.82 [95% CI, 3.70–3.95] per 100 patient-years) where as non-haemorrhagic stroke/SE occurred in 957 patients (rate, 1.00 [95% CI, 0.94–1.06] per 100 patient-years) and major bleed/haemorrhagic stroke in 935 patients (rate, 0.97 [95% CI, 0.91–1.04] per 100 patient-years). The cumulative incidence curves of the three outcomes across the 2 year follow-up period are shown in Figure S1.

Predictors of all-cause mortality, non-haemorrhagic stroke/SE and major bleeding

The following baseline variables were found to be significantly associated with all-cause mortality: age, sex, ethnicity, weight, diastolic blood pressure, pulse, CHF, CKD, vascular disease, diabetes, dementia, history of bleeding, prior stroke, treatment and smoking (Table 2a). The variables associated with non-haemorrhagic stroke/SE were: age, diastolic blood pressure, prior stroke, CKD, CHF, dementia, diabetes, vascular disease, history of bleeding, treatment and smoking (Table 2b). A higher risk of major bleeding was associated with older age, resting heart rate, CKD, diabetes, vascular disease, carotid occlusive disease, NOAC, VKA and AP treatments (Table 2b).

Patients who received NOAC and VKA therapies demonstrated a reduction of all-cause mortality and non-haemorrhagic stroke/SE and increased risk of major bleeding when compared with those that received no oral anticoagulant (NOAC: HR 0.66 (0.61-0.72), 0.56 (0.48-0.67), and 1.27 (1.05-1.55); VKA: HR 0.83 (0.77-0.90), 0.70 (0.61-0.81) and 1.84 (1.55-2.18) respectively). NOAC use was associated with lower risk of all-cause mortality, non-haemorrhagic stroke/SE, and major bleeding when compared with VKA.

Performance of GARFIELD-AF risk models, CHA_2DS_2-VASc or HAS-BLED in GARFIELD-AF patients

The GARFIELD-AF risk model for all-cause mortality, non-haemorrhagic stroke/SE and major bleeding is presented in figure 1. The GARFIELD-AF risk model for the all-cause mortality performed well in the overall population, AC treated, AC untreated, and in the lower risk groups; (C-index: 0.75, 0.74, 0.77 and 0.71, respectively). The GARFIELD-AF risk model for non-haemorrhagic stroke/SE and major bleeding also performed well in the overall population, AC treated, AC untreated and in the lower risk groups. The non-haemorrhagic

stroke/SE and bleeding model had an overall C-index of 0.68 (95% CI 0.67-0.70) and 0.68 (95% CI 0.66 to 0.70), respectively. A good calibration between predicted and observed all-cause mortality rates and an adequate calibration for non-haemorrhagic stroke/SE and major bleeding rates were observed. (Figure 2).

Comparison of the GARFIELD-AF, CHA_2DS_2-VASc or HAS-BLED risk scores

The performance of the GARFIELD-AF, CHA_2DS_2-VASc (or HAS-BLED for bleeding) risk models is shown in figure 1. The analyses demonstrate that the discriminatory value of the GARFIELD-AF integrated risk model was superior to CHA_2DS_2-VASc for all-cause mortality and non-haemorrhagic stroke/SE or HAS-BLED for major bleeding in the overall population, treated and untreated, as well as in the very low to low risk patients (CHA_2DS_2-VASc 0 or 1 for men and 1-2 for women/ HAS-BLED 0 or 1 for major bleeding / haemorrhagic stroke).

The GARFIELD-AF models provided additional information for all endpoints in the lower risk groups when compared with CHA_2DS_2-VASc or HAS-BLED. Whereas, CHA_2DS_2-VASc offered poor discrimination for mortality (C-index 0.52 (0.49-0.56)) and non-haemorrhagic stroke/SE (C-index 0.52 (0.46-0.58)) and HAS-BLED for bleeding (C-index 0.56 (0.55-0.58)) in low-risk group (Figure 1).

Internal validations

Internal validation of the GARFIELD-AF risk models at 2 year of follow-up is presented in supplementary table S1. The three models have a low change in the C-statistic after adjusting for fitting the models on the same dataset on which they were derived.

Distribution of CHA_2DS_2-VASc scores by GARFIELD-AF stroke score deciles

The distribution of CHA_2DS_2-VASc scores: (0 (men)/1 (women) for whom OAC should not be prescribed, 1 (men)/2 (women) for whom OAC should be considered and >1 (men)/>2 (women) for whom OAC should be prescribed for stroke prevention as per ESC guidelines) by GARFIELD-AF stroke score deciles are shown in figure 3. A high proportion of patients in the lowest two deciles of risk according to the GARFIELD-AF stroke scores would likely be treated with OACs based on the CHA_2DS_2-VASc scores. Up to 24% of very low risk patients (GARFIELD-AF 1st decile) were CHA_2DS_2-VASc ≥2 (excluding gender). As stroke risk increased according to GARFIELD-AF, the CHA_2DS_2-VASc score also increased. All high risk patients according to the GARFIELD-AF stroke score (10th decile) were CHA_2DS_2-VASc ≥2 (excluding gender).

The observed stroke incidence estimates by CHA_2DS_2-VASc score and GARFIELD-AF stroke risk category are presented in supplementary table S2. The GARFIELD-AF score shows additional increases in risk within each of the four groupings of the CHA_2DS_2-VASc score. For example, for patients with a CHA_2DS_2-VASc score of 2-3, the actual 2-year rate of non-haemorrhagic stroke/SE increases from 0.80 to 2.86 across the quartiles of GARFIELD-AF risk scores. This increase in risk across GARFIELD-AF risk quartiles is seen within each of the four CHA_2DS_2-VASc score categories. Correspondingly, this trend for increasing event rates is also true for increasing CHA_2DS_2-VASc scores within the two high quartiles of GARFIELD-AF risk. However, there seems to be little differentiation of risk, using CHA_2DS_2-VASc, when moving from 0-1 to 2-3 for the lowest quartile of risk or for 0-1 to 2-3 to 4-5 for the 2nd quartile of risk.

External validation of GARFIELD-AF risk models in the ORBIT-AF and Danish AF cohort

The external validation of the GARFIELD-AF risk model was done in ORBIT-AF, an independent population registry from the US registry and Danish AF cohort consisting of patients with AF derived from the Danish nationwide registries. The calibration plots for the GARFIELD-AF risk model in ORBIT-AF and Danish AF cohort for 2 year all-cause mortality, non-haemorrhagic stroke/SE and major bleeding are shown in figure S2 and Figure S3.

The predictive value of GARFIELD-AF risk models for all-cause mortality, non-haemorrhagic stroke/SE and major bleeding in patients enrolled in ORBIT-AF and Danish AF cohort is presented in Table 3. In both ORBIT-AF and Danish AF cohort, the performance of GARFIELD-AF risk model was good for all-cause mortality when compared to CHA_2DS_2-VASc and was comparable to CHA_2DS_2-VASc for the prediction of non-haemorrhagic stroke/SE.

In ORBIT-AF, the performance of GARFIELD-AF risk model was comparable to HAS-BLED score and in Danish AF cohort, the performance was better when compared to HAS-BLED in predicting bleeding.

Performance of the GARFIELD-AF risk models at different time points during follow-up in the GARFIELD-AF population

The C statistic at 30 days for all-cause mortality (C-index 0.80 (0.78-0.83)), non-haemorrhagic stroke/SE (C-index 0.71 (0.66-0.77)) and major bleeding (C-index 0.71 (0.66-0.77)) were slightly higher when compared to those at 1-year and 2-year follow-up (Table 4).

Web based GARFIELD-AF risk tool

The online GARFIELD-AF calculator is available from GARFIELD-AF website https://af.garfieldregistry.org/garfield-af-risk-calculator and a mobile app, Calculate by Qx-MD; https://qxmd.com/calculate/calculator_685/garfield-af-risk-calculator.

DISCUSSION

Previous findings from GARFIELD-AF showed a higher rate of early death and an increased risk of stroke/SE and bleeding during the first month after newly diagnosed AF (21). However, as revealed in this report, risks of death, stroke/SE and major bleeding increase over time. By 2 years, mortality risks are 3.8 fold greater than the risks of stroke/SE and of major bleeding. Awareness of this excess mortality risk may allow clinicians to address residual cardiovascular risk factors and lifestyle factors, more comprehensively (22). By incorporating risk prediction not only for stroke/SE but also for mortality, major bleeding, and the impact of anticoagulant treatment, the GARFIELD-AF predictor has the potential to enhance guideline-based treatment in AF.

The GARFIELD-AF new risk model for simultaneous prediction of mortality, non-haemorrhagic stroke/SE and major bleeding was superior to the existing risk scores for stroke and bleeding in AF patients over 2 years. The findings are consistent with, and they build upon, those reported for the GARFIELD-AF risk model at one year (4). The updated GARFIELD-AF tool now incorporates the impact of anticoagulant treatment (VKA or NOAC) or no anticoagulant.

Predictors of increased risk of all-cause mortality, non-haemorrhagic stroke/SE and major bleeding were older age, prior stroke, vascular disease, diabetes, CKD and history of bleeding were associated with higher risk of the three outcomes (mortality, non-haemorrhagic stroke/SE,

major bleeding). CHF, dementia and smoking were associated with mortality and non-haemorrhagic stroke/SE. Thought CKD, dementia and smoking are not the components of the CHA_2DS_2-VASc score, they had a strong influence on the risk of death and non-haemorrhagic stroke/SE. Similarly, CKD, vascular disease and carotid occlusive disease are not the components of the HAS-BLED but were associated with high risk of major bleeding. Those treated with a NOAC or a VKA exhibited a reduction of all-cause mortality and stroke/SE when compared with no OAC. NOAC treatment was associated with a lower risk of all-cause mortality, non-haemorrhagic stroke/SE and major bleeding when compared with VKA. These results were consistent with previous findings from GARFIELD-AF (23). Ethnicity was found to be an important predictor of the all-cause mortality but not for stroke/SE or major bleeding. Geographic variations were a powerful factor associated with outcomes as in the previous study (24). However, findings from GARFIELD-AF showed that geographic variations in outcome are not accounted for by differences in baseline characteristics (23).

The GARFIELD-AF model assesses multiple variables and incorporates anticoagulant treatment. It performed better than CHA_2DS_2-VASc for all-cause mortality. The CHA_2DS_2-VASc score covers the variables of congestive heart failure, hypertension, age of 75 years or older, diabetes mellitus Type II, previous stroke/transient ischaemic attack (TIA) or thromboembolism, vascular disease, age 65–74 years and female gender. However, other potential risk factors such as CKD, carotid occlusive disease, obesity, or smoking were not included in that model. R2CHADS2 or ATRIA scores to predict thromboembolic risk in patients with non-valvular AF include the variables ‘proteinuria’, ‘end-stage renal disease’, or ‘estimated glomerular filtration rate (eGFR) of below 45 mL/min’. These variables are useful for weighing the individual thromboembolic risk in intermediate-risk patients and thus can be considered for decision-making (25, 26).

The GARFIELD-AF integrated risk model was also superior to CHA_2DS_2-VASc for all-cause mortality and non-haemorrhagic stroke/SE or HAS-BLED for major bleeding in the very low to low risk patients (CHA_2DS_2-VASc 0 or 1 for men and 1-2 for women/ HAS-BLED 0 or 1 for major bleeding / haemorrhagic stroke). The distribution of CHA_2DS_2-VASc score categories by GARFIELD-AF stroke score deciles showed that the 24 of very low risk patients according to the GARFIELD-AF stroke scores would have been categorised as CHA_2DS_2-VASc $\geq$2 and hence, by current guidelines, indicated for anticoagulant treatment. The observed stroke risk remains constant as the CHA_2DS_2-VASc increases up to the 1st quartile of the population. However, using the GARFIELD-AF score, the incidence of stroke risk increased within this cohort. Thus, potentially, the GARFIELD-AF risk score could help clinicians apply the guideline recommendations. OAC use in low and very low risk patients remains contentious, and guidelines do not indicate a benefit for OAC treatment in such patients.

Web based risk tool

The GARFIELD-AF risk tool demonstrated good calibration and discrimination, outperforming CHA_2DS_2-VASc at predicting risk of death and non-haemorrhagic stroke/SE and HAS-BLED for bleeding in very low to low risk AF patients over 2 years. The online GARFIELD-AF calculator is available from GARFIELD-AF website https://af.garfieldregistry.org/garfield-af-risk-calculator and a mobile app, Calculate by Qx-MD; https://qxmd.com/calculate/calculator_685/garfield-af-risk-calculator..

Case Studies

To illustrate potential applications of the GARFIELD-AF risk predictor two brief case illustrations are provided (Figure 4a and 4b).

Case 1 (figure 4a)

Age: 62; Gender: Male; Weight: 70kg; Ethnicity: Asian; BP: 132/86 (not treated for hypertension); Diabetic; Renal dysfunction CrCl 45ml/min (moderate to severe); Smoker; Currently on NSAIDS for joint discomfort; Labile INR on warfarin and renal disease

Risk Scores

$CHA_2DS_2VASc = 1$

HAS-BLED =3 points

GARFIELD-AF risk for mortality: No OAC (4.1%), VKA (3.5%) and NOAC (2.8%)

GARFIELD-AF risk for Ischaemic Stroke/SE: No OAC (3.4%), VKA (2.4%) and NOAC (1.9%);

GARFIELD-AF risk for Major bleeding including Haemorrhagic stroke: No OAC (1.2%), VKA (2.2%) and NOAC (1.5%)

Treatment options

He would probably not anticoagulated with CHA_2DS_2VASc 1 and HAS-BLED 3 but the GARFIELD-AF risk scores show that the risk of death and stroke is potentially lower with anticoagulation than no treatment, and potentially lower bleeding risk in those treated with a NOAC when compared with VKA treatment.

Case 2 (figure 4b)

Age: 72; Gender: Female; Weight: 60kg; Ethnicity: Caucasian; BP: 142/86 (treated for hypertension); Early dementia; Renal dysfunction CrCl 50ml/min (moderate to severe); Currently on NOAC for AF

Risk Scores

$CHA_2DS_2VASc = 3$

HAS-BLED =2

GARFIELD-AF risk for mortality: No OAC (10.2%), VKA (8.5%) and NOAC (6.8%)

GARFIELD-AF risk for Ischaemic Stroke/SE: No OAC (4.2%), VKA (3.0%) and NOAC (2.4%)

GARFIELD-AF risk for Major bleeding including Haemorrhagic stroke: No OAC (1.6%), VKA (2.8%) and NOAC (2.0%)

Treatment options

This patient's CHA_2DS_2VASc stroke risk does not take the following risk predictors into consideration: she was on anticoagulation, BP142/86 with treated hypertension but not uncontrolled, age 72 (CHA_2DS_2VASc uses cut points for age, not continuous risk), renal dysfunction, early dementia.

The GARFIELD-AF risk scores show that the risks of death and stroke are potentially lower with NOAC treatment compared with VKA and No OAC treatment. The GARFIELD predictor indicates that the risks of bleeding are lower with NOACs than VKA treatment, but any anticoagulant treatment has higher bleeding risks than for no treatment.

Easily applicable tools for a personalised refinement of the individual thromboembolic risk in patients with AF and a CHA_2DS_2-VASc score of 1 guide clinicians through the question of whether to anticoagulate or not. Traditional risk assessment tools rely heavily on age, sex, and presence of cardiovascular comorbidities, but newer tools take into account changes in risk factors over time and novel biomarkers to facilitate more personalized risk assessment (27). These tools could be embedded into electronic medical record systems for point-of-care decision-making. They can be developed into applications for handheld electronic devices and for web-based interfaces.

Strengths and limitations of this study

The GARFIELD-AF risk model and risk tool were derived from the global prospective observational registry of patients with newly diagnosed atrial fibrillation (AF), for up to 2 years after enrolment. The GARFIELD-AF tool simultaneously calculates risks of death, non-haemorrhagic stroke/SE, and bleeding, based on OAC treatment selection, in a single calculation. The GARFIELD-AF risk score allows mortality to be assessed which give balance to the stroke and bleeding assessments. It also enables treatment effects to be estimated which is fundamentally different to CHA_2DS_2-VASc and HAS BLED.

The GARFIELD-AF risk tool was validated in the ORBIT-AF which includes patients with prevalent AF, whereas only new onset AF patients were enrolled in GARFIELD-AF. This external validation has limitations as information on carotid occlusive disease was not available in ORBIT-AF studies. The GARFIELD-AF risk tool was also validated in the national Danish AF registry and this analysis has limitations regarding the definitions of major bleeding. The Danish AF cohort selected ICD-10 codes for bleeding hospitalisations and GARFIELD-AF applied the ISTH criteria. In addition, it was not possible to ascertain ethnicity status in the

Danish cohort. The GARFIELD-AF tool is applicable to patients with atrial fibrillation, who in the view of the managing clinician, are at risk of stroke. Overall, 33.1% of patients in GARFIELD-AF did not receive anticoagulation so the tool is designed to provide a context for clinician/patient discussions about treatment choices. GARFIELD-AF excludes patients with non-AF indications for anticoagulation and it excludes patients with mechanical valves and severe valvular heart disease. An important limitation is that only baseline data were used in the risk assessment.

Clinical implications and future research directions:

The implications of this integrated GARFIELD-AF risk tool are several. First, it allows clinicians to perform a single calculation for mortality, stroke and bleeding and helps resolve the balanced considerations of risks and benefits. Second, it provides this information for both anticoagulated and non-anticoagulated patients, and the impact of NOAC versus VKA therapy. Third, it provides important data on mortality risk, thus highlighting the need for comprehensive secondary prevention. Forth, it provides more accurate risk prediction in low risk patients, a group were CHA_2DS_2-VASc and HAS-BLED do not perform well. Finally, application of this tool will help address the gap between guideline recommendations and clinical practice.

Acknowledgements

We thank the physicians, nurses and patients involved in the GARFIELD-AF registry. We thank Prof Gunnar H. Gislason, Department of Cardiology, Hertlev & Gentofte Hospital, Hellerup, Copenhagen, Denmark who provided Danish data for validations. Medical writing

support was provided by Dr Surekha Damineni (TRI, London, UK) and SAS programming support by Madhusudana Rao (TRI, London, UK).

Contributors

KAAF, JPB, AJC, DAF, SZG, SG, SH, WH, GK, FM, AO, JPP, AGGT, FWAV and AKK contributed to the study design. KAAF, AJC, JPB, DAF, GA, SZG, SG, AO, JPP and JP contributed to data acquisition. SV and KSP analyzed the data. All authors contributed to data interpretation. KAAF drafted the report. All authors critically reviewed the report and approved the final manuscript.

Funding

This work was supported by an unrestricted research grant from Bayer AG, Berlin, Germany, to TRI, London, UK, which sponsors the GARFIELD-AF registry. This work is supported by KANTOR CHARITABLE FOUNDATION for the Kantor-Kakkar Global Centre for Thrombosis Science.

Competing interests

KAAF reports grants and personal fees from Bayer, Janssen, and AstraZeneca; and has received personal fees from Sanofi/Regeneron and Verseon outside the submitted work. KSP reports personal fee from Thrombosis Research Institute, during the conduct of the study. J-PB reports none to disclose. AJC reports institutional grants and personal fees from Bayer, Boehringer Ingelheim, Pfizer/BristolMyers Squibb, and Daiichi-Sankyo, outside of the submitted work. DAF reports personal fees from Bayer outside the submitted work. SZG reports research support from BiO2 Medical, Boehringer Ingelheim, Bristol-Myers Squibb,

Boston Scientific, Daiichi-Sankyo, Janssen, National Heart, Lung, and Blood Institute, and the Thrombosis Research Institute; and has served as a consultant for Agile, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, Janssen, Portola, and Zafgen. SG reports has received personal fees from the Thrombosis Research Institute, and the American Heart Association; and has received grants from Sanofi, Ono, Bristol-Myers Squibb, the Vehicle Racing Commemorative Foundation, and Nakatani Foundation for Advancement of Measuring Technologies in Biomedical Engineering.outside the submitted work. SH reports personal personal fees from Aspen, Bayer, Bristol-Myers Squibb, Daiichi-Sankyo, Portola, and Sanofi outside of the submitted work. AO reports grants from Pfizer and personal fee from Medtronic, Boston Scientific, Daiichi, A. Menarini Research and Business Service GmbH and Bayer Healthcare Pharmaceuticals. FM is a former employee of Bayer AG. JPP receives grants for clinical research from Abbott, American Heart Association, Association for the Advancement of Medical Instrumentation, Bayer, Boston Scientific, and Philips and serves as a consultant to Abbott, Abbvie, Ablacon, Altathera, ARCA Biopharma, Biotronik, Boston Scientific, LivaNova, Medtronic, Milestone, Myokardia, ElectroPhysiology Frontiers, Pfizer, Respircardia, Sanofi, Philips, and Up-to-Date. AGGT reports has received grants from Bayer Healthcare; and has received personal fees from Bayer Healthcare, Bristol-Myers Squibb/Pfizer, Daiichi-Sankyo, and Boehringer Ingelheim.outside the submitted work. FWAV has received grants from Bayer Healthcare, and personal fees from Bayer Healthcare, BMS/Pfizer, Daiichi-Sankyo, and Boehringer-Ingelheim. AKK has received grants from Bayer AG and Sanofi; personal fees from Bayer AG, Janssen, Pfizer, Sanofi, Verseon and Anthos Therapeutics. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Ethical Approval

Independent ethics committee and hospital-based institutional review board approvals were obtained, as necessary, for the registry protocol.

Data sharing

The data underlying this article will be shared on reasonable request from Karen S Pieper (KPieper@tri-london.ac.uk).

Transparency

The lead authors affirm that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted.

Patient consent

Obtained.

References

1. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke. 1991;22(8):983-8.

2. Odutayo A, Wong CX, Hsiao AJ, Hopewell S, Altman DG, Emdin CA. Atrial fibrillation and risks of cardiovascular disease, renal disease, and death: systematic review and meta-analysis. BMJ. 2016;354:i4482.

3. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. European Heart Journal. 2020.

4. Fox KAA, Lucas JE, Pieper KS, Bassand J-P, Camm AJ, Fitzmaurice DA, et al. 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. BMJ Open. 2017;7(12):e017157.

5. Dalgaard F, Pieper K, Verheugt F, Camm AJ, Fox KA, Kakkar AK, et al. GARFIELD-AF model for prediction of stroke and major bleeding in atrial fibrillation: a Danish nationwide validation study. BMJ Open. 2019;9(11):e033283.

6. Zhu W, Fu L, Ding Y, Huang L, Xu Z, Hu J, et al. Meta-analysis of ATRIA versus CHA(2)DS(2)-VASc for predicting stroke and thromboembolism in patients with atrial fibrillation. International journal of cardiology. 2017;227:436-42.

7. Kakkar AK, Mueller I, Bassand JP, Fitzmaurice DA, Goldhaber SZ, Goto S, et al. International longitudinal registry of patients with atrial fibrillation at risk of stroke: Global Anticoagulant Registry in the FIELD (GARFIELD). Am Heart J. 2012;163(1):13-9 e1.

8. Kakkar AK, Mueller I, Bassand J-P, Fitzmaurice DA, Goldhaber SZ, Goto S, et al. Risk Profiles and Antithrombotic Treatment of Patients Newly Diagnosed with Atrial Fibrillation at Risk of Stroke: Perspectives from the International, Observational, Prospective GARFIELD Registry. PLoS ONE. 2013;8(5):e63479.

9. Marinigh R, Lip GY, Fiotti N, Giansante C, Lane DA. Age as a risk factor for stroke in atrial fibrillation patients: implications for thromboprophylaxis. J Am Coll Cardiol. 2010;56(11):827-37.

10. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest. 2010;138(5):1093-100.

11. Fox KAA, Gersh BJ, Traore S, Camm AJ, Kayani G, Krogh A, et al. Evolving quality standards for large-scale registries: the GARFIELD-AF experience. Eur Heart J Qual Care Clin Outcomes. 2017;3:114-22.

12. Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): the TRIPOD statement. Ann Intern Med. 2015;162(1):55-63.

13. Piccini JP, Fraulo ES, Ansell JE, Fonarow GC, Gersh BJ, Go AS, et al. Outcomes registry for better informed treatment of atrial fibrillation: rationale and design of ORBIT-AF. Am Heart J. 2011;162(4):606-12 e1.

14. Golwala H, Jackson LR, 2nd, Simon DN, Piccini JP, Gersh B, Go AS, et al. Racial/ethnic differences in atrial fibrillation symptoms, treatment patterns, and outcomes:

Insights from Outcomes Registry for Better Informed Treatment for Atrial Fibrillation Registry. Am Heart J. 2016;174:29-36.

15. Gundlund A, Fosbol EL, Kim S, Fonarow GC, Gersh BJ, Kowey PR, et al. Family history of atrial fibrillation is associated with earlier-onset and more symptomatic atrial fibrillation: Results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) registry. Am Heart J. 2016;175:28-35.

16. O'Brien EC, Kim S, Thomas L, Fonarow GC, Kowey PR, Mahaffey KW, et al. Clinical Characteristics, Oral Anticoagulation Patterns, and Outcomes of Medicaid Patients With Atrial Fibrillation: Insights From the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF I) Registry. Journal of the American Heart Association. 2016;5(5).

17. Kaatz S, Ahmad D, Spyropoulos AC, Schulman S. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. Journal of thrombosis and haemostasis : JTH. 2015;13(11):2119-26.

18. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2002;39(2 Suppl 1):S1-266.

19. Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013;44(7):2064-89.

20. Steinberg BA, Blanco RG, Ollis D, Kim S, Holmes DN, Kowey PR, et al. Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II: rationale and design of the ORBIT-AF II registry. Am Heart J. 2014;168(2):160-7.

21. Bassand JP, Virdone S, Goldhaber SZ, Camm AJ, Fitzmaurice DA, Fox KAA, et al. Early Risks of Death, Stroke/Systemic Embolism, and Major Bleeding in Patients With Newly Diagnosed Atrial Fibrillation. Circulation. 2019;139(6):787-98.

22. Escobar C, Camm AJ. Changing paradigms: from prevention of thromboembolic events to improved survival in patients with atrial fibrillation. Europace. 2020.

23. Bassand JP, Accetta G, Al Mahmeed W, Corbalan R, Eikelboom J, Fitzmaurice DA, et al. Risk factors for death, stroke, and bleeding in 28,628 patients from the GARFIELD-AF registry: Rationale for comprehensive management of atrial fibrillation. PLoS One. 2018;13(1):e0191592.

24. Fox K.A.A. AG, Darius H., Goto S., Kayani G., Koretsune Y., Oh S., Parkhomenko A., Sawhney J.P.S., Stepinska J., Kakkar A.K. Do baseline characteristics account for geographical variations in event rates in patients with newly diagnosed atrial fibrillation? The GARFIELD-AF registry. . Eur Heart J 2016;37:4100.

25. Piccini JP, Stevens SR, Chang Y, Singer DE, Lokhnygina Y, Go AS, et al. Renal dysfunction as a predictor of stroke and systemic embolism in patients with nonvalvular atrial fibrillation: validation of the R(2)CHADS(2) index in the ROCKET AF (Rivaroxaban Once-daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation) and ATRIA (AnTicoagulation and Risk factors In Atrial fibrillation) study cohorts. Circulation. 2013;127(2):224-32.

26. Singer DE, Chang Y, Borowsky LH, Fang MC, Pomernacki NK, Udaltsova N, et al. A new risk scheme to predict ischemic stroke and other thromboembolism in atrial fibrillation: the ATRIA study stroke risk score. J Am Heart Assoc. 2013;2(3):e000250.

27. Pallazola VA, Kapoor RK, Kapoor K, McEvoy JW, Blumenthal RS, Gluckman TJ. Anticoagulation risk assessment for patients with non-valvular atrial fibrillation and venous thromboembolism: A clinical review. Vasc Med. 2019;24(2):141-52.

Figure Legend

Figure 1. Comparison of the performance (C-statistic (95% CI) of the GARFIELD-AF risk models versus CHA_2DS_2-VASc (for (a) all-cause mortality and (b) non-haemorrhagic stroke/SE) or (c) HAS-BLED (for major bleeding/haemorrhagic stroke) at two years of follow-up in the whole GARFIELD-AF population and by baseline anticoagulation and risk category

Very low to low risk: CHA_2DS_2-VASc score of 0 or 1 (men) and 1 or 2 (women); HAS-BLED 0 or 1 for major bleeding / haemorrhagic stroke.

Figure 2. Calibration of GARFIELD-AF risk models for all-cause mortality (a), non-haemorrhagic stroke/SE (b), and major bleeding/haemorrhagic stroke (c) at 2 years of follow-up in the GARFIELD-AF population

Figure 3. Distribution of CHA_2DS_2-VASc score categories by GARFIELD-AF stroke score deciles

Figure 4a and b. GARFIELD-AF online Risk calculator

Table 1. Baseline characteristics for the whole study population and by outcome. Events are not mutually exclusive.

Variable	All patients (N = 52,032)	Outcome occurred within 2 years		
		Death (N = 3702)	Non-haemorrhagic stroke / SE (N = 957)	Major bleeding / haemorrhagic stroke (N = 935)
Sex, n (%)				
Male	29,042 (55.8)	2018 (54.5)	481 (50.3)	490 (52.4)
Female	22,989 (44.2)	1684 (45.5)	476 (49.7)	445 (47.6)
Age, median (Q1; Q3), years	71.0 (63.0; 78.0)	78.0 (71.0; 84.0)	75.0 (68.0; 81.0)	76.0 (69.0; 82.0)
Age, n (%), years				
<65	15,961 (30.2)	459 (12.4)	165 (17.2)	130 (13.9)
65-69	8019 (15.4)	360 (9.7)	119 (12.4)	109 (11.7)
70-74	8929 (17.2)	534 (14.4)	175 (18.3)	162 (17.3)
≥75	19,393 (37.3)	2349 (63.5)	498 (52.0)	534 (57.1)
Ethnicity, n (%)				
Caucasian	32,005 (63.1)	2503 (61.2)	600 (64.4)	646 (71.7)
Hispanic/Latino	3392 (6.7)	311 (8.6)	72 (7.7)	56 (6.2)
Asian	14,282 (28.1)	685 (19.0)	229 (24.6)	181 (20.1)
Afro-Caribbean/Mixed/Other	1069 (2.1)	105 (2.9)	31 (3.3)	18 (2.0)
Body mass index, median (Q1; Q3), kg/m²	26.9 (23.9; 30.7)	26.0 (22.8; 30.1)	26.7 (23.8; 30.1)	26.5 (23.3; 30.7)
Systolic blood pressure, median (Q1; Q3), mmHg	130.0 (120.0; 145.0)	130.0 (119.0; 143.0)	135.0 (120.0; 150.0)	133.0 (120.0; 145.0)
Diastolic blood pressure, median (Q1; Q3), mmHg	80.0 (70.0; 88.0)	79.0 (70.0; 85.0)	80.0 (70.0; 90.0)	80.0 (70.0; 88.0)
Pulse, median (Q1; Q3), bpm	84.0 (70.0; 105.0)	88.0 (73.0; 110.0)	85.0 (72.0; 108.0)	87.0 (72.0; 110.0)
Type of atrial fibrillation, n (%)				

Permanent	6630 (12.7)	627 (16.9)	139 (14.5)	110 (11.8)
Persistent	7758 (14.9)	508 (13.7)	146 (15.3)	123 (13.2)
Paroxysmal	14,307 (27.5)	734 (19.8)	224 (23.4)	226 (24.2)
New onset (unclassified)	23,331 (44.8)	1833 (49.5)	448 (46.8)	476 (50.9)
Care setting specialty at diagnosis, n (%)				
Internal medicine	9370 (18.0)	852 (23.0)	222 (23.2)	197 (21.1)
Cardiology	34,187 (65.7)	2227 (60.2)	543 (56.7)	545 (58.3)
Neurology	874 (1.7)	81 (2.2)	40 (4.2)	32 (3.4)
Geriatrics	202 (0.4)	41 (1.1)	8 (0.8)	4 (0.4)
Primary care/general practice	7393 (14.2)	501 (13.5)	144 (15.0)	157 (16.8)
Care setting location at diagnosis, n (%)				
Hospital	30,341 (58.3)	2357 (63.7)	599 (62.6)	530 (56.7)
Office	15,581 (29.9)	924 (25.0)	247 (25.8)	249 (26.6)
Anticoagulation clinic/thrombosis centre	339 (0.7)	24 (0.6)	8 (0.8)	6 (0.6)
Emergency room	5536 (10.7)	397 (10.7)	103 (10.8)	150 (16.0)
Medical history, n (%)				
Congestive heart failure	11,739 (22.6)	1466 (39.6)	272 (28.4)	216 (23.1)
Coronary artery disease	11,253 (21.6)	1168 (31.6)	270 (28.2)	247 (26.4)
Acute coronary syndromes	5536 (10.7)	653 (17.8)	153 (16.1)	155 (16.6)
Coronary artery bypass graft	1625 (3.2)	190 (5.2)	43 (4.5)	51 (5.6)
Stenting	3542 (6.9)	342 (9.3)	78 (8.2)	103 (11.1)
Vascular disease	12,818 (24.8)	1365 (37.2)	310 (32.6)	296 (31.9)
Carotid occlusive disease	1544 (3.0)	157 (4.3)	37 (3.9)	52 (5.7)
Pulmonary embolism/deep vein thrombosis	1354 (2.6)	149 (4.1)	34 (3.6)	29 (3.1)
Prior stroke	3878 (7.5)	421 (11.4)	163 (17.0)	99 (10.6)
Prior transient ischaemic attack	2267 (4.4)	225 (6.1)	76 (8.0)	59 (6.5)
Prior systemic embolism	334 (0.6)	31 (0.8)	8 (0.8)	11 (1.2)
Prior bleeding	1316 (2.5)	204 (5.5)	43 (4.5)	54 (5.8)
Hypertension	39,610 (76.3)	2853 (77.3)	780 (81.7)	739 (79.4)
Hypercholesterolaemia	20,959 (41.6)	1425 (40.1)	423 (46.2)	410 (44.7)
Diabetes	11,546 (22.2)	1022 (27.6)	256 (26.8)	253 (27.1)
Cirrhosis	294 (0.6)	48 (1.3)	4 (0.4)	9 (1.0)

Moderate to severe CKD	5355 (11.7)	830 (25.3)	171 (20.7)	195 (22.8)
Dementia	764 (1.5)	187 (5.1)	39 (4.1)	15 (1.6)
Hyperthyroidism	898 (1.8)	60 (1.7)	15 (1.6)	24 (2.6)
Hypothyroidism	3035 (6.0)	252 (7.0)	52 (5.6)	56 (6.0)
Alcohol consumption, n (%)				
Abstinent	24,447 (55.5)	1965 (62.5)	462 (56.1)	420 (54.6)
Light	14,364 (32.6)	905 (28.8)	267 (32.4)	261 (33.9)
Moderate	4184 (9.5)	200 (6.4)	70 (8.5)	68 (8.8)
Heavy	1026 (2.3)	72 (2.3)	24 (2.9)	20 (2.6)
Smoking status, n (%)				
Non-smoker	31,023 (65.4)	2059 (61.1)	576 (64.6)	525 (61.9)
Ex-smoker	11,203 (23.6)	978 (29.0)	206 (23.1)	241 (28.4)
Current smoker	5198 (11.0)	335 (9.9)	109 (12.2)	82 (9.7)
Treatment at baseline, n (%)				
NOAC ± AP	14,123 (27.5)	835 (22.9)	204 (21.7)	231 (25.3)
VKA ± AP	20,183 (39.3)	1463 (40.2)	351 (37.3)	468 (51.3)
AP only	10,761 (21.0)	871 (23.9)	269 (28.6)	129 (14.3)
None	6240 (12.2)	473 (13.0)	117 (12.4)	85 (9.3)
CHA_2DS_2-VASc score, median (Q1; Q3)	3.0 (2.0; 4.0)	4.0 (3.0; 5.0)	4.0 (3.0; 5.0)	4.0 (3.0; 5.0)
HAS-BLED score, median (Q1; Q3)[1]	1.0 (1.0; 2.0)	2.0 (1.0; 2.0)	2.0 (1.0; 2.0)	2.0 (1.0; 2.0)

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

Table 2a. Wald Chi-square, p-values and hazard ratios for components of the GARFIELD all-cause mortality model

All-cause mortality model	Chi-square	P-value	Hazard Ratio (95% CI)
Age[1]	956	<.0001	
up to 65 years			1.17 (1.11-1.23)
65 years or older			1.38 (1.35-1.42)
Congestive heart failure	403	<.0001	2.00 (1.87-2.14)
Ethnicity (ref.: Caucasian)	197	<.0001	
Hispanic/Latino			1.17 (1.04-1.32)
Asian			0.54 (0.49-0.60)
Afro-Caribbean/Mixed/Other			1.46 (1.20-1.77)
Diastolic blood pressure (up to 80 mmHg)[1]	100	<.0001	0.91 (0.89-0.93)
Weight (up to 75 kg)[1]	98	<.0001	0.90 (0.88-0.92)
Pulse (up to 120 bpm)[1]	96	<.0001	1.04 (1.03-1.05)
Moderate to severe CKD	89	<.0001	1.46 (1.35-1.58)
Treatment (ref.: No OAC)	89	<.0001	
NOAC			0.66 (0.61-0.72)
VKA			0.83 (0.77-0.90)
Vascular disease	74	<.0001	1.36 (1.27-1.46)
Female sex	71	<.0001	0.74 (0.69-0.79)
Diabetes	55	<.0001	1.32 (1.23-1.43)
Dementia	40	<.0001	1.63 (1.40-1.90)
Current smoker	36	<.0001	1.41 (1.26-1.58)
History of bleeding	28	<.0001	1.47 (1.27-1.70)
Prior stroke	26	<.0001	1.31 (1.18-1.45)

[1]Hazard ratios with 95% confidence intervals are based on incremental units of '5'

Table 2b. Wald Chi-square, p-values and hazard ratios for components of the GARFIELD non-haemorrhagic stroke/SE and major bleeding models

Model	Chi-square	P-value	Hazard Ratio (95% CI)
Non-haemorrhagic stroke/SE model			
Age[1]	132	<.0001	1.22 (1.18-1.26)
Prior stroke	84	<.0001	2.23 (1.88-2.64)
Treatment (ref.: No OAC)	49	<.0001	
NOAC			0.56 (0.48-0.67)
VKA			0.70 (0.61-0.81)
Current smoker	22	<.0001	1.61 (1.32-1.97)
Diastolic blood pressure (80 mmHg or more)[1]	20	<.0001	1.08 (1.05-1.12)
Moderate to severe CKD	17	<.0001	1.42 (1.20-1.67)
Congestive heart failure	10	0.0015	1.26 (1.09-1.46)
Dementia	9	0.0022	1.67 (1.20-2.32)
Diabetes	8	0.0041	1.24 (1.07-1.43)
Vascular disease	8	0.0057	1.22 (1.06-1.40)
History of bleeding	3	0.0555	1.35 (0.99-1.83)
Major bleeding			
Age[1]	156	<.0001	1.24 (1.20-1.29)
Treatment (ref.: No OAC)	56	<.0001	
NOAC			1.27 (1.05-1.55)
VKA			1.84 (1.55-2.18)
Moderate to severe CKD	36	<.0001	1.65 (1.40-1.94)
History of bleeding	31	<.0001	2.19 (1.66-2.88)
Pulse (bpm)[1]	12	0.0005	1.02 (1.01-1.03)
AP treatment (ref.: no AP treatment)	9	0.0021	1.27 (1.09-1.47)
Diabetes	6	0.0176	1.19 (1.03-1.38)
Vascular disease	5	0.0250	1.18 (1.02-1.37)
Carotid occlusive disease	5	0.0281	1.37 (1.03-1.82)

[1]Hazard ratios with 95% confidence intervals are based on incremental units of '5'

Table 3. Evaluation of the performance (C-statistic (95% CI)) of the GARFIELD-AF risk models versus CHA_2DS_2-VASc (for all-cause mortality and non-haemorrhagic stroke/SE) or HAS-BLED (for major bleeding/haemorrhagic stroke) at two years of follow-up in the ORBIT-AF study population and Danish AF cohort.

	ORBIT-AF		**Danish AF Cohort**	
	GARFIELD-AF	**CHA_2DS_2-VASc/HAS-BLED***	**GARFIELD-AF**	**CHA_2DS_2-VASc/HAS-BLED***
All-cause mortality	0.75 (0.74-0.76)	0.68 (0.67-0.69)	0.77(0.77-0.78)	0.68 (0.67-0.68)
Non-haemorrhagic stroke/SE	0.68 (0.64-0.71)	0.67 (0.64-0.71)	0.69(0.68-0.69)	0.66 (0.65-0.67)
Major bleeding/haemorrhagic stroke	0.64 (0.62-0.66)	0.63 (0.61-0.64)*	0.67(0.66-0.68)	0.63 (0.61-0.64)*

ORBIT-AF: History of bleeding and carotid occlusive disease were not available; Danish AF Cohort: Blood pressure, BMI, pulse, smoking and ethnicity were not available

Table 4. Evaluation of the performance (C-statistic (95% CI)) of the GARFIELD risk models at different time points during follow-up in the GARFIELD-AF population

Model	Time of follow-up		
	30 days	1 year	2 years
All-cause mortality	0.80 (0.78-0.83)	0.76 (0.75-0.77)	0.75 (0.74-0.76)
Non-haemorrhagic stroke/SE	0.71 (0.66-0.77)	0.70 (0.68-0.72)	0.68 (0.67-0.70)
Major bleeding/hemorrhagic stroke	0.71 (0.66-0.77)	0.69 (0.67-0.71)	0.68 (0.66-0.70)

Figure 1

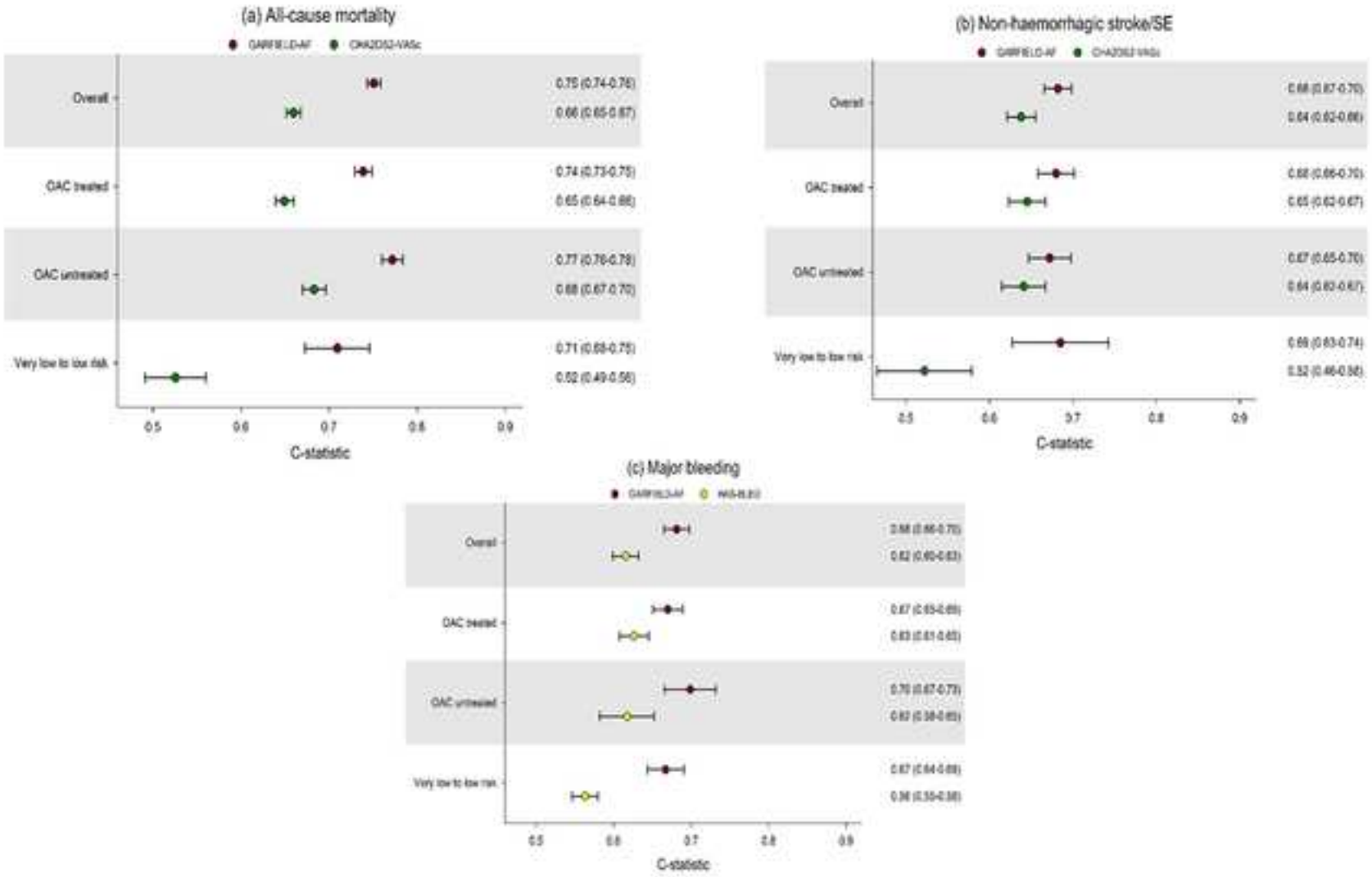

Figure 2

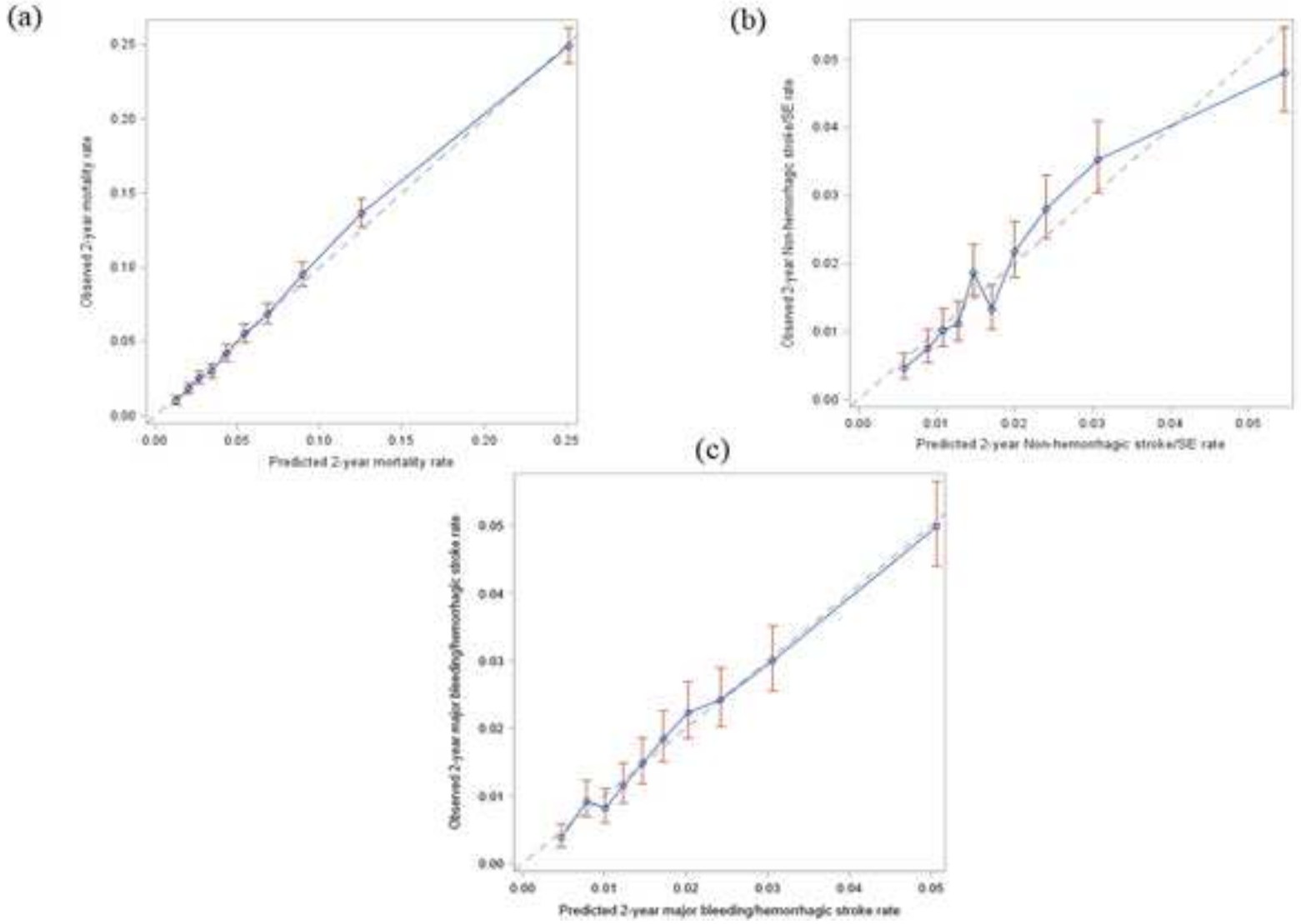

Figure 3

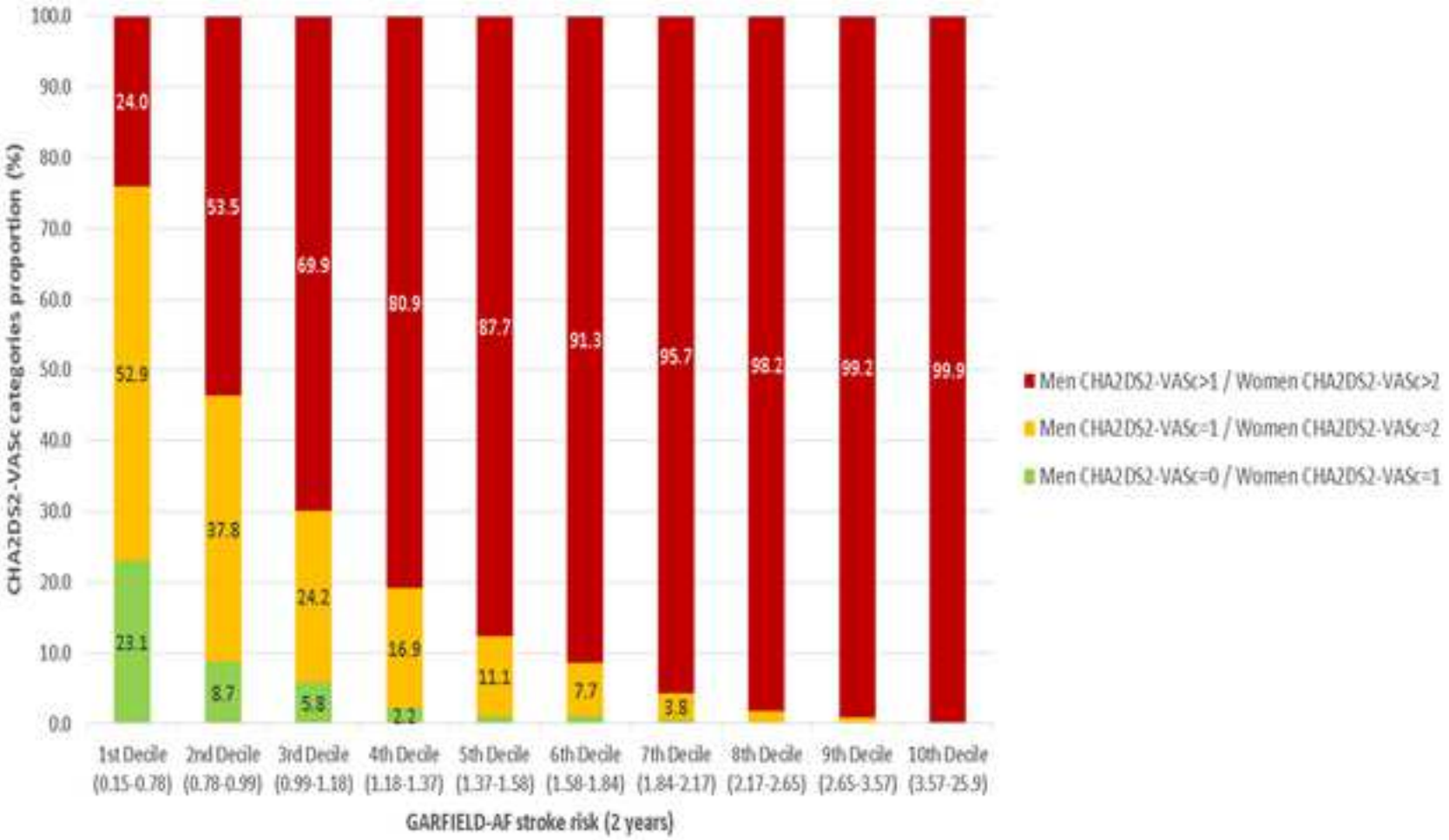

Figure 4

Graphical Abstract