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

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Aims
To determine whether the Global Anticoagulant Registry in the FIELD–Atrial Fibrillation (GARFIELD-AF) integrated risk tool predicts mortality, non-haemorrhagic stroke/systemic embolism, and major bleeding for up to 2 years after new-onset AF and to assess how this risk tool performs compared with CHA2DS2-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 methods. Indices were evaluated in comparison with CHA2DS2-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 CHA2DS2-VASc for all-cause mortality in all cohorts. The GARFIELD-AF risk score was superior to CHA2DS2-VASc for non-haemorrhagic stroke, and it outperformed HAS-BLED for major bleeding in internal validation and in the Danish AF cohort. In very low- to low-risk patients [CHA2DS2-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 CHA2DS2-VASc and HAS-BLED. The GARFIELD-AF tool also included the effect of oral anticoagulation (OAC) therapy, thus allowing clinicians to compare the expected outcome of different anticoagulant treatment decisions [i.e. no OAC, non-vitamin K antagonist (VKA) oral anticoagulants, or VIKs].

Conclusions
The GARFIELD-AF risk tool outperformed CHA2DS2-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.
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**Keywords**
- GARFIELD-AF
- CHA$_2$DS$_2$-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. The 2018 ESC guidelines for the diagnosis and management of AF suggest using the CHA₂DS₂-VASc risk score to identify patients at low risk (CHA₂DS₂-VASc score = 0 in men, or 1 in women) for whom antithrombotic therapy should not be prescribed. Oral anticoagulation (OAC) should be prescribed for stroke prevention in patients with CHA₂DS₂-VASc score ≥2 in men, or ≥3 in women and should considered in patients with a CHA₂DS₂-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.

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 (CHA₂DS₂-VASc) and bleeding (HAS-BLED). The nationwide Danish AF cohort provides external validation and indicates that the GARFIELD-AF model is superior to CHA₂DS₂-VASc in predicting stroke/systemic embolism (SE) and is comparable with HAS-BLED for predicting major bleeding. Integrated clinical scores like GARFIELD-AF and other scores which incorporate biomarker measurement demonstrate statistically significant though numerically modest improvement in the prediction of stroke risk when compared to CHA₂DS₂-VASc.

In this report, we aimed (i) to derive and validate a new risk model for predicting mortality, non-haemorrhagic stroke/SE, and major bleeding up to 2 years after enrolment based on treatment selection. (ii) 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 1818 sites) 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. In brief, baseline characteristics included patient characteristics, medical history, care settings, type of AF, date and method of diagnosis, symptoms of AF, and type of anticoagulant treatment [VKAs, factor Xa inhibitors and direct thrombin inhibitors, as well as antiplatelet treatment (AP)]. Data on components of the CHA₂DS₂-VASc and HAS-BLED risk stratification schemes were also collected to assess the risks of non-haemorrhagic stroke and major bleeding. Collection of follow-up data occurred at four monthly intervals based on telephone interviews and hospital records up to 24 months. The incidence of ischaemic stroke, transient ischaemic attack (TIA), SE, acute coronary syndrome, hospitalization, 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, and data were examined for completeness and accuracy by the coordinating centre (TRI, London, UK). By design, 20% of all electronic case report forms 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 2 years follow-up were censored at 2 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/SE, 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.

Comparisons of the performance of the new GARFIELD-AF risk models were made with (i) CHA₂DS₂-VASc score (for all-cause mortality, non-haemorrhagic stroke/SE) and (ii) 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 CHA₂DS₂-VASc score in discriminating patients with a low stroke risk. We considered a CHA₂DS₂-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 CHA₂DS₂-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.

Definitions

Non-haemorrhagic stroke/SE was defined as the combined endpoints of ischaemic stroke, unknown-type stroke, SE, and TIA. Major bleed was classified by investigators according to the International Society on Thrombosis and Haemostasis (ISTH) definition. Major bleeds, including intracranial bleeds, were defined as a combined endpoint of haemorrhagic stroke and any major bleed. Minor/non-major clinically relevant 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. 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: moderate-to-severe, or mild or none. Congestive heart failure was defined as current/prior history of CHF or left ventricular ejection fraction of <40%. Standard clinical definitions of stroke and TIA were
used. Acute coronary syndrome included unstable angina, ST-elevation myocardial infarction (STEMI), and non-STEMI.

The CHA2DS2-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 SE. The HAS-BLED score was the sum of points after addition of one point each for uncontrolled hypertension (systolic blood pressure >160 mmHg), moderate-to-severe CKD, cirrhosis, stroke history, bleeding history, elderly (>65), and heavy alcohol use (fluctuations in international normalized 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 regression. The predictors were selected from the list of potential predictors (Supplementary material online, List S1).

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 (HR) estimates with 95% confidence interval (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 (CHA2DS2-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 tool in two external populations: the ORBIT-AF registry (ORBIT-AF I and ORBIT-AF II) 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 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], hospitalization or outpatient visit, were included from 1 January 2010 until 1 August 2015 with follow-up to 1 August 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. ICD-10 codes and Anatomical Therapeutic Chemical (ATC) codes were used as described in the previous publication.6 Additional codes were used for Carotid occlusion (D1625), diabetes (ICD-10, E10, E11, ATC-codes: A10A, A10B), and dementia (ICD-10: F00, F02, F01, F039, G30, ATC-code: N06D). For unavailable variables like blood pressure, body mass index, 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 (interquartile range) age was 71.0 (63.0–78.0) 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 Supplementary material online, Figure S1.

Predictors of all-cause mortality, non-haemorrhagic stroke/systemic embolism, 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 2). The variables associated with non-haemorrhagic stroke/SE
Table 1  Baseline characteristics for the whole study population and by outcome

| Variables                                      | All patients (N = 52 032) | Outcome occurred within 2 years | Major bleeding/haemorrhagic stroke (N = 935) |
|------------------------------------------------|---------------------------|----------------------------------|-----------------------------------------------|
| Sex, n (%)                                     |                           |                                  |                                               |
| Male                                           | 29 042 (55.8)             | 2018 (54.5)                      | 481 (50.3)                                    |
| Female                                         | 22 989 (44.2)             | 1684 (45.5)                      | 476 (49.7)                                    |
| Age (years), median (Q1–Q3)                    | 71.0 (63.0–78.0)          | 78.0 (71.0–84.0)                 | 75.0 (68.0–81.0)                              |
| Age (years), n (%)                             |                           |                                  |                                               |
| <65                                            | 15 961 (30.2)             | 459 (12.4)                       | 165 (17.2)                                    |
| 65–69                                          | 8019 (15.4)               | 360 (9.7)                        | 119 (12.4)                                    |
| 70–74                                          | 8929 (17.2)               | 534 (14.4)                       | 175 (18.3)                                    |
| ≥75                                            | 19 393 (37.3)             | 2349 (63.5)                      | 498 (52.0)                                    |
| Ethnicity, n (%)                               |                           |                                  |                                               |
| Caucasian                                      | 32 005 (63.1)             | 2503 (61.2)                      | 600 (64.4)                                    |
| Hispanic/Latino                                | 3392 (6.7)                | 311 (8.6)                        | 72 (7.7)                                      |
| Asian                                          | 14 282 (28.1)             | 685 (19.0)                       | 229 (24.6)                                    |
| Afro-Caribbean/Mixed/Other                     | 1069 (2.1)                | 105 (2.9)                        | 31 (3.3)                                      |
| Body mass index (kg/m²), median (Q1–Q3)        | 26.9 (23.9–30.7)          | 26.0 (22.8–30.1)                 | 26.7 (23.8–30.1)                              |
| Systolic blood pressure (mmHg), median (Q1–Q3) | 130.0 (120.0–145.0)       | 130.0 (119.0–143.0)              | 135.0 (120.0–150.0)                           |
| Diastolic blood pressure (mmHg), median (Q1–Q3)| 80.0 (70.0–88.0)          | 79.0 (70.0–85.0)                 | 80.0 (70.0–90.0)                              |
| Pulse (b.p.m.), median (Q1–Q3)                 | 84.0 (70.0–105.0)         | 88.0 (73.0–110.0)                | 85.0 (72.0–108.0)                             |
| Type of atrial fibrillation, n (%)             |                           |                                  |                                               |
| Permanent                                      | 6630 (12.7)               | 627 (16.9)                       | 139 (14.5)                                    |
| Persistent                                     | 7758 (14.9)               | 508 (13.7)                       | 146 (15.3)                                    |
| Paroxysmal                                     | 14 307 (27.5)             | 734 (19.8)                       | 224 (23.4)                                    |
| New onset (unclassified)                       | 23 331 (44.8)             | 1833 (49.5)                      | 448 (46.8)                                    |
| Care setting specialty at diagnosis, n (%)     |                           |                                  |                                               |
| Internal medicine                              | 9370 (18.0)               | 852 (23.0)                       | 222 (23.2)                                    |
| Cardiology                                     | 34 187 (65.7)             | 2227 (60.2)                      | 543 (56.7)                                    |
| Neurology                                      | 874 (1.7)                 | 81 (2.2)                         | 40 (4.2)                                      |
| Geriatrics                                     | 202 (0.4)                 | 41 (1.1)                         | 8 (0.8)                                       |
| Primary care/general practice                  | 7393 (14.2)               | 501 (13.5)                       | 144 (15.0)                                    |
| Care setting location at diagnosis, n (%)      |                           |                                  |                                               |
| Hospital                                       | 30 341 (58.3)             | 2357 (63.7)                      | 599 (62.6)                                    |
| Office                                         | 15 581 (29.9)             | 924 (25.0)                       | 247 (25.8)                                    |
| Anticoagulation clinic/thrombosis centre       | 339 (0.7)                 | 24 (0.6)                         | 8 (0.8)                                       |
| Emergency room                                 | 5536 (10.7)               | 397 (10.7)                       | 103 (10.8)                                    |
| Medical history, n (%)                         |                           |                                  |                                               |
| Congestive heart failure                       | 11 739 (22.6)             | 1466 (39.6)                      | 272 (28.4)                                    |
| Coronary artery disease                        | 11 253 (21.6)             | 1168 (31.6)                      | 270 (28.2)                                    |
| Acute coronary syndromes                       | 5536 (10.7)               | 653 (17.8)                       | 153 (16.1)                                    |
| Coronary artery bypass graft                   | 1625 (3.2)                | 190 (5.2)                        | 43 (4.5)                                      |
| Stenting                                       | 3542 (6.9)                | 342 (9.3)                        | 78 (8.2)                                      |
| Vascular disease                               | 12 818 (24.8)             | 1365 (37.2)                      | 310 (32.6)                                    |
| Carotid occlusive disease                      | 1544 (3.0)                | 157 (4.3)                        | 37 (3.9)                                      |
| Pulmonary embolism/deep vein thrombosis        | 1354 (2.6)                | 149 (4.1)                        | 34 (3.6)                                      |
| Prior stroke                                   | 3878 (7.5)                | 421 (11.4)                       | 163 (17.0)                                    |
| Prior transient ischaemic attack               | 2267 (4.4)                | 225 (6.1)                        | 76 (8.0)                                      |
| Prior systemic embolism                        | 334 (0.6)                 | 31 (0.8)                         | 8 (0.8)                                       |
| Prior bleeding                                 | 1316 (2.5)                | 204 (5.5)                        | 43 (4.5)                                      |
| Hypertension                                   | 39 610 (76.3)             | 2853 (77.3)                      | 780 (81.7)                                    |
| Hypercholesterolaemia                          | 20 959 (41.6)             | 1425 (40.1)                      | 423 (46.2)                                    |
| Diabetes                                       | 11 546 (22.2)             | 1022 (27.6)                      | 256 (26.8)                                    |
| Cirrhosis                                      | 294 (0.6)                 | 48 (1.3)                         | 4 (0.4)                                       |

Continued
Table 1  Continued

| Variables                                                                 | 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) |
| 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)   |
| CHA₂DS₂-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)*                                         | 1.0 (1.0–2.0)             | 2.0 (1.0–2.0)                     | 2.0 (1.0–2.0)                                 | 2.0 (1.0–2.0) |

Events are not mutually exclusive.
AP, antplatelet treatment; SE, systemic embolism.
*aThe 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).

were age, diastolic blood pressure, prior stroke, CKD, CHF, dementia, diabetes, vascular disease, history of bleeding, treatment, and smoking (Table 3). 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 3).

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 who 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, CHA₂DS₂-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 0.66–0.70), 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, CHA₂DS₂-VASc, or HAS-BLED risk scores

The performance of the GARFIELD-AF, CHA₂DS₂-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 CHA₂DS₂-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 (CHA₂DS₂-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 CHA₂DS₂-VASc or HAS-BLED. Whereas, CHA₂DS₂-VASc offered poor discrimination for mortality [C-index 0.52 (0.49–0.56)], non-
The distribution of \( \text{CH}_2 \text{DS}_2 \text{-VASc} \) scores by \( \text{GARFIELD-AF} \) stroke score deciles

The distribution of \( \text{CH}_2 \text{DS}_2 \text{-VASc} \) 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 \( \text{GARFIELD-AF} \) stroke score deciles are shown in Figure 3. A high proportion of patients in the lowest two deciles of risk according to the \( \text{GARFIELD-AF} \) stroke scores would likely be treated with OACs based on the \( \text{CH}_2 \text{DS}_2 \text{-VASc} \) scores. Up to 24% of very low-risk patients (\( \text{GARFIELD-AF} \) 1st decile) were \( \text{CH}_2 \text{DS}_2 \text{-VASc} \geq 2 \) (excluding gender). As stroke risk increased according to \( \text{GARFIELD-AF} \), the \( \text{CH}_2 \text{DS}_2 \text{-VASc} \) score also increased. All high-risk patients according to the \( \text{GARFIELD-AF} \) stroke score (10th decile) were \( \text{CH}_2 \text{DS}_2 \text{-VASc} \geq 2 \) (excluding gender).

The observed stroke incidence estimates by \( \text{CH}_2 \text{DS}_2 \text{-VASc} \) score and \( \text{GARFIELD-AF} \) stroke risk category are presented in Supplementary material online, Table S2. The \( \text{GARFIELD-AF} \) score shows additional increases in risk within each of the four groupings of the \( \text{CH}_2 \text{DS}_2 \text{-VASc} \) score. For example, for patients with a \( \text{CH}_2 \text{DS}_2 \text{-VASc} \) 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 \( \text{GARFIELD-AF} \) risk scores. This increase in risk across \( \text{GARFIELD-AF} \) risk quartiles is seen within each of the four \( \text{CH}_2 \text{DS}_2 \text{-VASc} \) score categories. Correspondingly, this trend for increasing event rates is also true for increasing \( \text{CH}_2 \text{DS}_2 \text{-VASc} \) scores within the two high quartiles of \( \text{GARFIELD-AF} \) risk. However, there seems to be little differentiation of risk, using \( \text{CH}_2 \text{DS}_2 \text{-VASc} \), 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.

**Table 2** Wald \( \chi^2 \), P-values, and hazard ratios for components of the \( \text{GARFIELD-AF} \) all-cause mortality model

| All-cause mortality model       | \( \chi^2 \) | P-value | Hazard ratio (95% CI) |
|--------------------------------|-------------|---------|----------------------|
| Age*                          | 956         | <0.0001 | 1.17 (1.11–1.23)      |
| Up to 65 years                |             |         | 1.38 (1.35–1.42)      |
| 65 years or older             |             |         | 1.56 (1.53–1.59)      |
| Congestive heart failure      | 403         | <0.0001 | 2.00 (1.87–2.14)      |
| Ethnicity (ref.: Caucasian)   | 197         | <0.0001 | 1.17 (1.11–1.23)      |
| Hispanic/Latino               |             |         | 1.04 (1.03–1.05)      |
| Asian                         |             |         | 0.90 (0.88–0.92)      |
| Afro-Caribbean/Mixed/Other    |             |         | 0.54 (0.49–0.60)      |
| Diastolic blood pressure (up to 80 mmHg)* | 100         | <0.0001 | 0.83 (0.77–0.90)      |
| Weight (up to 75 kg)*         | 98          | <0.0001 | 0.91 (0.89–0.93)      |
| Pulse (up to 120 b.p.m.)*     | 96          | <0.0001 | 0.90 (0.88–0.92)      |
| Moderate-to-severe CKD        | 89          | <0.0001 | 1.46 (1.35–1.58)      |
| Treatment (ref.: no OAC)      | 89          | <0.0001 | 1.04 (1.03–1.05)      |
| NOAC                          |             |         | 0.90 (0.88–0.92)      |
| VKA                           |             |         | 0.54 (0.49–0.60)      |
| Vascular disease              | 74          | <0.0001 | 1.36 (1.27–1.46)      |
| Female sex                    | 71          | <0.0001 | 0.74 (0.69–0.79)      |
| Diabetes                      | 55          | <0.0001 | 1.32 (1.23–1.43)      |
| Dementia                      | 40          | <0.0001 | 1.63 (1.40–1.90)      |
| Current smoker                | 36          | <0.0001 | 1.41 (1.26–1.58)      |
| History of bleeding           | 28          | <0.0001 | 1.47 (1.27–1.70)      |
| Prior stroke                  | 26          | <0.0001 | 1.31 (1.18–1.45)      |

CI, confidence interval; CKD, chronic kidney disease; NOAC, non-VKA oral anticoagulant; OAC, oral anticoagulation; VKA, vitamin K antagonist.

*Hazard ratios with 95% CIs are based on incremental units of ‘5’.

Internal validation of the \( \text{GARFIELD-AF} \) risk models at 2-year of follow-up is presented in Supplementary material online, Table S1. The three models have a low change in the C-statistic after adjusting for the models on the same dataset on which they were derived.
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 4. In both ORBIT-AF and Danish AF cohort, the performance of GARFIELD-AF risk model was good for all-cause mortality when compared to CHA²DS²-VASc and was comparable to CHA²DS²-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 the 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- and 2-year follow-up (Table 5).

### Table 3: Wald χ², P-values, and hazard ratios for components of the GARFIELD-AF non-haemorrhagic stroke/SE and major bleeding models

| Model                      | χ²   | P-value | Hazard ratio (95% CI) |
|----------------------------|------|---------|-----------------------|
| Non-haemorrhagic stroke/SE model |
| Age                        | 132  | <0.0001 | 1.22 (1.18–1.26)       |
| Prior stroke               | 84   | <0.0001 | 2.23 (1.88–2.64)       |
| Treatment (ref.: no OAC)   | 49   | <0.0001 |                       |
| NOAC                       |      |         | 0.56 (0.48–0.67)       |
| VKA                        |      |         | 0.70 (0.61–0.81)       |
| Current smoker             | 22   | <0.0001 | 1.61 (1.32–1.97)       |
| Diastolic blood pressure (80 mmHg or more) | 20 | <0.0001 | 1.08 (1.05–1.12)       |
| Moderate-to-severe CKD     | 17   | <0.0001 | 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                        | 156  | <0.0001 | 1.24 (1.20–1.29)       |
| Treatment (ref.: no OAC)   | 56   | <0.0001 |                       |
| NOAC                       |      |         | 1.27 (1.05–1.55)       |
| VKA                        |      |         | 1.84 (1.55–2.18)       |
| Moderate-to-severe CKD     | 36   | <0.0001 | 1.65 (1.40–1.94)       |
| History of bleeding        | 31   | <0.0001 | 2.19 (1.66–2.88)       |
| Pulse (b.p.m.)             | 12   | 0.0005  | 1.02 (1.01–1.03)       |
| Moderate-to-severe CKD     |      |         | 1.27 (1.09–1.47)       |
| Carotid occlusive disease  | 5    | 0.0176  | 1.19 (1.03–1.38)       |
| AP treatment (ref.: no AP treatment) | 9 | 0.0021 | 1.18 (1.02–1.37)       |
| AP treatment (ref.: no AP treatment) | 5 | 0.0250 | 1.37 (1.03–1.82)       |

AP, antplatelet treatment; CI, confidence interval; CKD, chronic kidney disease; NOAC, non-VKA oral anticoagulant; OAC, oral anticoagulation; SE, systemic embolism; VKA, vitamin K antagonist.

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](https://af.garfieldregistry.org/garfield-af-risk-calculator) and a mobile app, Calculate by Qx-MD; [https://qxmd.com/calculator/calculator_685/garfield-af-risk-calculator](https://qxmd.com/calculator/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. 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. 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 1 year. 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). Congestive heart failure, dementia, and smoking were associated with mortality and non-haemorrhagic stroke/SE. Though CKD, dementia, and smoking are not the components of the CHA\textsuperscript{2}DS\textsuperscript{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 an 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. 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. However, findings from GARFIELD-AF showed that geographic variations in outcome are not accounted for by differences in baseline characteristics.

The GARFIELD-AF model assesses multiple variables and incorporates anticoagulant treatment. It performed better than CHA\textsuperscript{2}DS\textsuperscript{2}-VASc for all-cause mortality. The CHA\textsuperscript{2}DS\textsuperscript{2}-VASc score covers the variables of CHF, hypertension, age of 75 years or older, diabetes mellitus Type II, previous stroke/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 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.

The GARFIELD-AF integrated risk model was also superior to CHA²DS²-VASc for all-cause mortality and non-haemorrhagic stroke/systemic embolism (SE) or HAS-BLED for major bleeding in the very low- to low-risk patients (CHA²DS²-VASc 0 or 1 for men and 1–2 for women/HAS-BLED 0 or 1 for major bleeding/haemorrhagic stroke). The distribution of CHA²DS²-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 categorized as CHA²DS²-VASc ≥2 and hence, by current guidelines, indicated for anticoagulant treatment. The observed stroke risk remains constant as the CHA²DS²-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. Oral anticoagulation 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 CHA²DS²-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

**Figure 2** Calibration of GARFIELD-AF risk models for all-cause mortality (A), non-haemorrhagic stroke/systemic embolism (B), and major bleeding/haemorrhagic stroke (C) at 2 years of follow-up in the GARFIELD-AF population. SE, systemic embolism.
Case 1 (Figure 4A)
Age: 62; Gender: Male; Weight: 70 kg; Ethnicity: Asian; BP: 132/86 (not treated for hypertension); Pulse: 80 bpm; Diabetic; Renal dysfunction CrCl 45 mL/min (moderate to severe); Smoker; Currently on NSAIDS for joint discomfort; Labile INR on warfarin and renal disease.

Risk scores
CHA\textsubscript{2}-DS\textsubscript{2}-VASc = 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\textsubscript{2}-DS\textsubscript{2}-VASc 1 and HAS-BLED 3 but the GARFIELD-AF risk scores show that the risk of death and stroke are potentially lower with anticoagulation than no treatment, and potentially lower bleeding risk in those treated with an NOAC when compared with VKA treatment.

Case 2 (Figure 4B)
Age: 72; Gender: Female; Weight: 60 kg; Ethnicity: Caucasian; BP: 142/86 (treated for hypertension); Pulse: 80 bpm; Early dementia; Renal dysfunction CrCl 50 mL/min (moderate to severe); Currently on NOAC for AF.

Risk scores
CHA\textsubscript{2}-DS\textsubscript{2}-VASc = 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\textsubscript{2}-DS\textsubscript{2}-VASc stroke risk does not take the following risk predictors into consideration: she was on anticoagulation, BP 142/86 with treated hypertension but not uncontrolled, age 72 (CHA\textsubscript{2}-DS\textsubscript{2}-VASc 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.

Figure 3 Distribution of CHA\textsubscript{2}-DS\textsubscript{2}-VASc score categories by GARFIELD-AF stroke score deciles. GARFIELD-AF, Global Anticoagulant Registry in the FIELD–Atrial Fibrillation.
Table 4  Evaluation of the performance [C-statistic (95% CI)] of the GARFIELD-AF risk models vs. CHA2DS2-VASc (for all-cause mortality and non-haemorrhagic stroke/SE) or HAS-BLED (for major bleeding/haemorrhagic stroke) at 2 years of follow-up in the ORBIT-AF study population and Danish AF cohort

|                | ORBIT-AF      | ORBIT-AF | CHA2DS2-VASc/ HAS-BLED | ORBIT-AF | ORBIT-AF | CHA2DS2-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. BMI, body mass index; CI, confidence interval; GARFIELD-AF, Global Anticoagulant Registry in the FIELD–Atrial Fibrillation; SE, systemic embolism.

Table 5  Evaluation of the performance [C-statistic (95% CI)] of the GARFIELD-AF 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/haemorrhagic stroke | 0.71 (0.66–0.77) | 0.69 (0.67–0.71) | 0.68 (0.66–0.70) |

CI, confidence interval; GARFIELD-AF, Global Anticoagulant Registry in the FIELD–Atrial Fibrillation; SE, systemic embolism.

Figure 4  (A and B) GARFIELD-AF online risk calculator. NOAC, non-VKA oral anticoagulant; OAC, oral anticoagulation; VKA, vitamin K antagonist.
app. calculate by Qx-MD: https://qxmd.com/calculator/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 B).

Easily applicable tools for a personalized refinement of the individual thromboembolic risk in patients with AF and a CHA2DS2-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 CHA2DS2-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 hospitalizations 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 vs. VKA therapy. Third, it provides important data on mortality risk, thus highlighting the need for comprehensive secondary prevention. Fourth, it provides more accurate risk prediction in low-risk patients, a group were CHA2DS2-VASc and HAS-BLED do not perform well. Finally, application of this tool will help address the gap between guideline recommendations and clinical practice.

Supplementary material
Supplementary material is available at European Heart Journal – Quality of Care and Clinical Outcomes online.

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**Ethical approval**

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

**Data availability**

The data and model equations underlying this article will be shared on reasonable request from Karen S. Pieper (kpieper@bri-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.

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