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Harry Gibbs PhD , Ben Freedman PhD , Mårten Rosenqvist PhD ,
Saverio Virdone MSc , Wael Al Mahmeed MD ,
Giuseppe Ambrosio MDPhD , A. John Camm MD ,
Barry Jacobson MD , Carlos Jerjes-Sanchez MD , Gloria Kayani ,
Ali Oto MD , Elizaveta Panchenko PhD , Hany Ragy MD ,
Ajay K. Kakkar PhD , for the GARFIELD-AF Investigators

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Clinical Significance

- Major adverse outcomes of non-hemorrhagic stroke, death and major bleeding do not differ between asymptomatic and symptomatic presentations of atrial fibrillation.

- Adverse outcomes in asymptomatic and symptomatic atrial fibrillation presentations are comparably reduced by oral anticoagulation.

- Opportunistic screening in everyday practice to detect asymptomatic atrial fibrillation may be beneficial as it likely has the same prognosis as asymptomatic atrial fibrillation at presentation and likely responds similarly to oral anticoagulation.

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Clinical outcomes in asymptomatic and symptomatic atrial fibrillation presentations in GARFIELD-AF: Implications for atrial fibrillation screening

†Harry Gibbs, PhD,[1] †Ben Freedman, PhD,[2] Mårten Rosenqvist, PhD,[3] Saverio Virdone, MSc,[4] Wael Al Mahmeed, MD,[5] Giuseppe Ambrosio, MD, PhD,[6] A. John Camm, MD,[7] Barry Jacobson, MD,[8] Carlos Jerjes-Sanchez, MD,[9] Gloria Kayani,[4] Ali Oto, MD,[10] Elizaveta Panchenko, PhD,[11] Hany Ragy, MD,[12] Ajay K. Kakkar, PhD[4,13]; for the GARFIELD-AF Investigators*

*A full list of GARFIELD-AF investigators is provided in the supplemental material

†Harry Gibbs and Ben Freedman contributed equally

[1]The Alfred Hospital, Melbourne, VIC, Australia

[2]Heart Research Institute, Charles Perkins Centre, and Sydney School of Medicine, University of Sydney, Sydney, NSW, Australia

[3]Karolinska Institutet, Danderyd University Hospital, Stockholm, Sweden

[4]Thrombosis Research Institute, London, UK

[5]Heart and Vascular Institute, Cleveland Clinic Abu Dhabi, Abu Dhabi, United Arab Emirates

[6]University of Perugia School of Medicine, Perugia, Italy

[7]St George's University of London, London, UK

[8]Johannesburg Hospital, University of the Witwatersrand, Johannesburg, South Africa

[9]Escuela de Medicina y Ciencias de la Salud. Tecnologico de Monterrey. Instituto de Cardiologia y Medicina Vascular, TEC Salud, Mexico

[10]Hacettepe University, Ankara, Turkey

[11]Cardiology Research and Production Center, Moscow, Russia

[12]Hayat Hospital, Cairo, Egypt

[13]University College London, London, UK

Corresponding author:

Professor Ben Freedman

The Heart Research Institute

7 Eliza St Newtown

Sydney, NSW 2042

Australia.

Email: ben.freedman@sydney.edu.au

ABSTRACT

Background: Asymptomatic atrial fibrillation is often detected incidentally. Prognosis and optimal therapy for asymptomatic compared to symptomatic atrial fibrillation is uncertain. This study compares clinical characteristics, treatment, and 2-year outcomes of asymptomatic and symptomatic atrial fibrillation presentations.

Methods: GARFIELD-AF is a global, prospective, observational study of newly diagnosed atrial fibrillation with ≥ 1 stroke risk factors (http://www.clinicaltrials.gov. Unique identifier: NCT01090362). Patients were characterized by atrial fibrillation-related symptoms at presentation and the congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65-74 years, sex (CHA_2DS_2-VASc) score. Two-year follow-up recorded anticoagulation patterns (vitamin K antagonist [VKAs], direct oral anticoagulants [DOACs], parenteral therapy) and outcomes (stroke/systemic embolism, all-cause mortality, and bleeding).

Results: At presentation, 52,032 eligible patients, 25.4% were asymptomatic, and 74.6% symptomatic. Asymptomatic patients were slightly older (72 vs. 70 years), more often male (64.2% vs. 52.9%), and more frequently initiated on anticoagulation ± antiplatelets (AP) (69.4% vs. 66.0%). No difference in events (adjusted hazard ratios, 95% CI) for non-hemorrhagic stroke/systemic embolism (1.19, 0.97-1.45), all-cause mortality (1.06, 0.94-1.20), or bleeding (1.02, 0.87-1.19) was observed. Anticoagulation was associated with comparable reduction in non-hemorrhagic stroke/systemic embolism (0.59, 0.43–0.82 vs. 0.78, 0.65–0.93) and all-cause mortality (0.69, 0.59-0.81 vs. 0.77, 0.71-0.85) (asymptomatic vs symptomatic, respectively).

Conclusions: Major outcomes do not differ between asymptomatic and symptomatic atrial fibrillation presentations and are comparably reduced by anticoagulation. Opportunistic screening-detected asymptomatic atrial fibrillation likely has the same prognosis as asymptomatic atrial fibrillation at presentation, and likely responds similarly to anticoagulation thrombo-prophylaxis.

Key words: Atrial fibrillation, asymptomatic, symptomatic, anticoagulation.

Atrial fibrillation is the commonest sustained cardiac arrhythmia in adults and is associated with an elevated risk of ischemic stroke, heart failure, cognitive impairment, hospitalisations, and death [1-4]. Many patients with atrial fibrillation present with recognizable symptoms or complications such as palpitations, stroke or heart failure, however, approximately one third of cases are diagnosed with no or non-specific symptoms (i.e. asymptomatic) [5-11]. These patients are frequently detected during physical examinations for other conditions, routine preoperative assessments, health checks (including blood pressure or pulse examination), or more recently, when participating in atrial fibrillation surveillance programs [12-15].

Opportunistic or systematic screening for asymptomatic atrial fibrillation could involve significant resource costs [16,17]. This, however, could be justified if the patients identified were high-risk individuals eligible for initiation of an oral anticoagulant (OAC) [18-23], potentially preventing stroke or premature mortality. Cost–benefit balance is largely determined by actual risk of stroke or death in asymptomatic presentations whether detected incidentally [24] or via an opportunistic screening program as recommended by guidelines and consensus documents [25-27].

Previous studies, which have been mostly retrospective in design, small scale, or have not been limited to asymptomatic patient presentation, have indicated that patients with "silent atrial fibrillation" have similar prognosis to those with symptomatic atrial fibrillation, showing comparable mortality, ischemic stroke, and bleeding [6,28-30]. Two studies have suggested that asymptomatic atrial fibrillation may be associated with an increase in all-cause mortality[8,31] and stroke[31] compared to atrial fibrillation with typical symptoms. Whether OAC therapy, encompassing both Vitamin K antagonists (VKAs) and direct oral anticoagulants (DOAC) exerts comparable beneficial effects in asymptomatic and symptomatic atrial fibrillation patients remains uncertain, although pivotal randomized trials of antithrombotic therapies have included a considerable, yet unknown, proportion of asymptomatic patients [32].

The Global Anticoagulant Registry in the FIELD-Atrial Fibrillation (GARFIELD-AF) study was designed prospectively to investigate outcomes in a large cohort of patients with newly diagnosed atrial fibrillation. The aim of the present analysis was to compare clinical characteristics, patterns of treatment, and 2-year outcomes in GARFIELD-AF stratified by the presence of asymptomatic or symptomatic disease at baseline.

METHODS

GARFIELD-AF study design

The design of GARFIELD-AF has been reported elsewhere [33,34]. Eligible men and women (≥18 years) were diagnosed with non-valvular atrial fibrillation, according to standard local procedures, within 6 weeks prior to entry to the registry. All eligible patients required at least one additional risk factor for stroke, as judged by local investigators, to be considered eligible for inclusion. Between 2010 and 2016, five separate cohorts of patients were enrolled prospectively and consecutively in 35 countries. Study sites represent the different care settings in each participating country (office-based practice; hospital departments including neurology, cardiology, geriatrics, internal medicine, and emergency; anticoagulation clinics; and general practice). Independent ethics committee and hospital-based institutional review board approvals were obtained. A list of central ethics committees and regulatory authorities that provided approval can be found in online (e-Appendix 1). The registry is conducted in accordance with the principles of the Declaration of Helsinki, local regulatory requirements, and International Conference on Harmonization–Good Pharmacoepidemiological and Clinical Practice guidelines. Written informed consent was obtained from all study participants, and their confidentiality and anonymity are maintained.

Procedures and outcome measures

Clincal characteristics documented at baseline included medical history, care setting, type of atrial fibrillation, date and method of diagnosis, symptoms, antithrombotic treatment, and cardiovascular drug prescriptions. In addition, data on components of the congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack (TIA), vascular disease, age 65 to 74 years, sex category (CHA_2DS_2-VASc) and the hypertension, abnormal liver/renal function, stroke history, bleeding history or predisposition, labile INR, elderly, drug/alcohol usage (HAS-BLED) risk stratification schemes were

collected. Collection of follow-up data was performed every 4 months up to 2-years after

enrolment. Data were captured by electronic case report forms (eCRFs). Submitted data were

examined for completeness and accuracy by the coordinating center (Thrombosis Research

Institute, London, UK); for quality control, 20% of eCRFs were automatically monitored

against source documentation. Data used for the present analysis were extracted in November

2018.

Patients were considered symptomatic if they had at least one of the following clinical

features documented at baseline: palpitations, shortness of breath, chest pain/discomfort,

dizziness, tiredness, sweating, or fainting; those with signs such as irregular pulse and/or

tachycardia but no symptoms were considered asymptomatic.

Statistical analysis

Baseline characteristics are presented for asymptomatic and symptomatic patients.

Continuous variables are summarized as medians (1st and 3rd quartile) and categorical

variables as absolute frequencies (percent). Event rates were estimated as the number of

events per 100 person years. Only the first occurrence of each event/patient was considered.

A multivariable Cox proportional hazard model was applied to estimate hazard ratios (HRs)

for association between symptoms at diagnosis and outcomes.

Propensity score methodology was adopted to allow for balanced comparison between

treatment groups (i.e. OAC versus no OAC). To control for balance covariate differences an

overlap weighting scheme was applied, which optimizes efficiency of comparisons by

defining the population with the highest overlap in covariates between treatment groups. The

underlying propensity score, calculated as the probability for receiving OAC, was obtained

using a logistic regression model including a large range of demographic and clinical

covariates (e-Table 1). Weights were subsequently applied to a Cox proportional hazards

model to estimate OAC effects on selected clinical endpoints within each of the two groups.

Treatment was defined as that initiated on enrollment, approximating "intention to treat."

Patients with missing values were not removed from the study; single imputation was applied

in comparative effectiveness analysis. All statistical analyses were performed using SAS$^{®}$

9.4.

RESULTS

Patients

Of the 52,080 enrolled patients, 52,032 had complete follow-up information. Of these, 13,235

patients (25.4%) were asymptomatic and 38,797 patients (74.6%) presented with symptoms

(Figure 1). Compared with the symptomatic group, asymptomatic patients were more likely

male, older, and to have suffered prior stroke, but had a lower prevalence of heart failure, and

vascular disease (Table 1). The two groups had similar median CHA_2DS_2-VASc and HAS-

BLED scores. Asymptomatic patients were more likely than symptomatic patients to be

diagnosed in the office (43% vs 25%, P<0.001), and less likely to be diagnosed in hospital or

emergency room (56% vs 74%, P<0.001).

Distribution of symptoms by type

Among newly diagnosed atrial fibrillation patients presenting with symptoms, palpitation was

the most common, accounting for 51.7% symptoms, followed by shortness of breath (41.6%)

and chest pain/discomfort (25.9%) (patients may have complained of more than 1 symptom).

Other documented symptoms included tiredness (18.9%), dizziness (16.0%), sweating

(5.6%), and fainting (5.3%),

Treatment pattern

Approaches for stroke prophylaxis in asymptomatic and symptomatic atrial fibrillation

patients, stratified by baseline CHA_2DS_2-VASc score <2 and ≥2, are portrayed in Figure 2a

and 2b, respectively. A slightly larger proportion of asymptomatic patients received OACs ±

antiplatelets (AP) compared to symptomatic patients (P<0.001). In the lower-risk group

(CHA$_2$DS$_2$-VASc <2), 58.5% of asymptomatic and 52.2% of symptomatic patients received OAC drugs; in the higher-risk group (CHA$_2$DS$_2$-VASc ≥2), 71.4% of asymptomatic and 68.5% of symptomatic patients received oral anticoagulation. Asymptomatic patients were less likely to receive AP therapy alone in comparison to symptomatic patients in both the low risk (20.6% vs 24.4%, respectively) and high risk (17.5% vs. 21.6%, respectively) categories. Patients who were not initiated on anticoagulation were comparable between the two groups.

Clinical outcomes over 2-years

Two-year incidence event rates for all-cause mortality, non-hemorrhagic stroke or systemic embolism, and major bleeding in asymptomatic and symptomatic atrial fibrillation and corresponding HRs (95% CIs) are shown in Figure 3. Unadjusted and adjusted HRs revealed no significant differences in the rates of the three outcomes in asymptomatic versus symptomatic atrial fibrillation patients.

Results of comparative effectiveness analyses of OAC (VKA or DOAC) versus no OAC for all-cause mortality, non-hemorrhagic stroke/systemic embolism and, major bleeding in asymptomatic and symptomatic atrial fibrillation patients are shown in Figure 4a–c. No difference was discernible in atrial fibrillation symptoms (present or absent) on effectiveness of these medications over time. Significant risk reductions in stroke/systemic embolism with OAC use were demonstrated in both groups (asymptomatic: HR, 0.59; 95% CI, 0.43–0.82; symptomatic: HR, 0.78; 95% CI, 0.65–0.93), as well as in all-cause mortality (asymptomatic: HR, 0.69; 95% CI, 0.59-0.81; symptomatic: HR, 0.77; 95% CI, 0.71-0.85). Both demonstrated an increased risk for major bleeding with OAC use (HR, 1.20; 95% CI, 0.85–1.68 and HR, 1.54; 95% CI, 1.24–1.90, respectively), although it only reached statistical significance in the symptomatic patients.

D

ISCUSSION

Comparing 13,235 asymptomatic and 38,797 symptomatic GARFIELD-AF-registered patients over a long-term duration of 2-years, few differences were observed among outcomes experienced or treatment received over time. There was no significant difference in stroke rates or mortality over 2-years between asymptomatic and symptomatic presentations of atrial fibrillation, nor in bleeding rates experienced. Given the likely similarity between asymptomatic patients with incidental atrial fibrillation clinical presentations, and those detected by opportunistic screening, our findings suggest that opportunistic atrial fibrillation screening programs might be worthwhile. An additional reason to justify screening is that asymptomatic atrial fibrillation presentations seem to respond similarly to OAC therapy as symptomatic atrial fibrillation.

Approximately half of asymptomatic and symptomatic patients with CHA_2DS_2-VASc score <2 and two-thirds of those with CHA_2DS_2-VASc score ≥2 received OAC drugs, with a slightly higher treatment rate in asymptomatic than symptomatic patients, irrespective of stroke risk category. An important finding was that asymptomatic and symptomatic subsets of patients responded equally well to OAC drugs in respect of reduction in ischemic stroke or systemic embolism, and with similar increased risk of major bleeding observed on these agents in both symptom groups. Unfortunately, large numbers of at-risk asymptomatic and symptomatic patients received no treatment, or AP only, despite the relative inefficacy of AP in preventing atrial fibrillation-related stroke – as has been observed by others [35,36].

Among GARFIELD-AF patients, one quarter were asymptomatic and three quarters had atrial fibrillation symptoms. Almost identical results were reported by the PREFER in atrial fibrillation [21] and ORBIT-AF [37] registries. The European Society of Cardiology (ESC)'s Euro Heart Survey on Atrial Fibrillation [38] also showed that approximately one-third of atrial fibrillation patients were asymptomatic and two-thirds were symptomatic on survey entry.

There were few clinical differences between asymptomatic and symptomatic patients, apart from the former being more likely to be male and to have had prior stroke, and the latter to have a greater burden of heart failure. Similar observations on the predominance of male sex have been consistently reported in other series [6,21,38-40]. One possible but unquantifiable difference between the groups is the duration of atrial fibrillation prior to enrollment. Patients with symptomatic atrial fibrillation may have presented with atrial fibrillation of shorter duration compared to those with asymptomatic atrial fibrillation, however both groups had atrial fibrillation first diagnosed within 6 weeks of enrollment. In a recent patient-level meta-analysis of single time-point screening for unknown atrial fibrillation in over 140,000 individuals, males predominated over females in all age strata [19] and in the AFFIRM study male sex accounted for 77% of asymptomatic patients [6]. AFFIRM also found that asymptomatic patients were more likely to have had prior stroke and were less likely to have coronary artery disease and heart failure. The finding of higher rates of prior stroke in asymptomatic patients is possibly explained by a greater burden of untreated atrial fibrillation, as those with symptoms may be more likely to present and receive earlier OAC. Symptomatic patients in our study were also significantly more likely to report smoking habits and pulmonary disease than asymptomatic counterparts.

Implementing screening programs in primary care has been suggested [41]. Numerous attempts have been made to discover optimal methods for detecting silent atrial fibrillation in the community [42]; these screening techniques may be described as systematic (mass invitation sent to target population, e.g. elderly individuals with risk factors) [23,43-45] or opportunistic (testing in patients attending a physician visit for any reason) [13,46-48]. Additionally, in patients with symptoms consistent with paroxysmal atrial fibrillation, a clinically-indicated search for atrial fibrillation may be advised using similar techniques and technologies. Nearly all screening efforts to date have aimed to bypass time-consuming conventional 12-lead

electrocardiogram (ECG) recordings with easier diagnostic methods using ECG handheld devices, from wearable recorders to invasively implanted loop recorders [49]. The advisability of ECG screening for atrial fibrillation was recently considered in a systematic literature review conducted by the US Preventive Services Task Force [50,51]. This study concluded that screening using either ECG or pulse palpation identified higher numbers of asymptomatic adults with newly discovered atrial fibrillation than did no screening, however, there was insufficient information to recommend for or against ECG screening.

In the present study, patients were not identified by mass screening. Therefore, asymptomatic cases were likely captured incidentally whereas symptomatic individuals were likely diagnosed when seeking treatment for symptoms consistent with atrial fibrillation. This would explain why many more asymptomatic cases than symptomatic cases presented in the office, rather than in hospital or Emergency Room. Our main findings that asymptomatic and symptomatic patients fared equivalently in terms of major adverse outcomes, and response to OAC therapy, supports guideline and consensus recommendation for conducting opportunistic screening in everyday clinical practice [26,27,52].

Limitations

This prospective registry study has limitations. Patients were dichotomized into asymptomatic and symptomatic groups on the basis of complaints typical of atrial fibrillation at baseline. Symptom resolution or subsequent development of new or intermittent symptoms may have occurred, but was not recorded over time, however we were primarily interested in the prognosis according to symptomatic status at diagnosis. Patients recorded as asymptomatic within GARFIELD-AF presented within 6 weeks of entry into the registry and thus symptomatic status is recorded somewhat later than patients who are detected by an opportunistic screening program. Whereas follow-up was conducted over 2-years, a relatively short time-frame for patients with a lifelong cardiac condition like atrial fibrillation,

this is mitigated by the first year after diagnosis having the highest risk in patients with atrial fibrillation [53-55]. We also have complete and verifiable data collected in a very large group of patients, which increases the robustness of the findings. Although we adjusted for all covariates available when comparing outcomes between those with and without symptoms, and responses to OAC vs no OAC prescription, it is possible that residual confounding factors may be present.

CONCLUSION

In this analysis of the large, global GARFIELD-AF registry 2-year clinical outcomes did not differ, and prescription of antithrombotic therapies was similar among asymptomatic and symptomatic atrial fibrillation patients at presentation. Our study also showed that asymptomatic patients had a similar response to OAC therapy as symptomatic individuals. As patients who are asymptomatic at clinical presentation likely have incidentally-detected atrial fibrillation, their prognosis and response to OAC therapy could be expected to mirror that of opportunistic screening-detected asymptomatic atrial fibrillation. These findings therefore support a likely benefit of screening across populations at risk for "silent atrial fibrillation."

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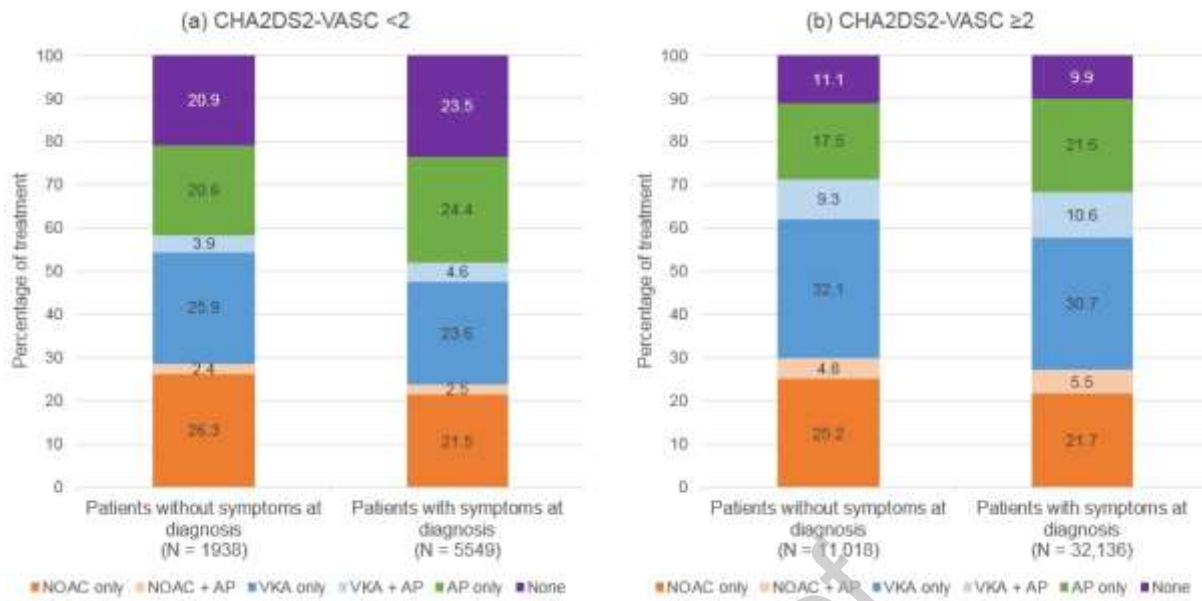
Figures

Title: Clinical outcomes in asymptomatic and symptomatic atrial fibrillation patients in

**GARFIELD-AF: Implications for atrial fibrillation screening**
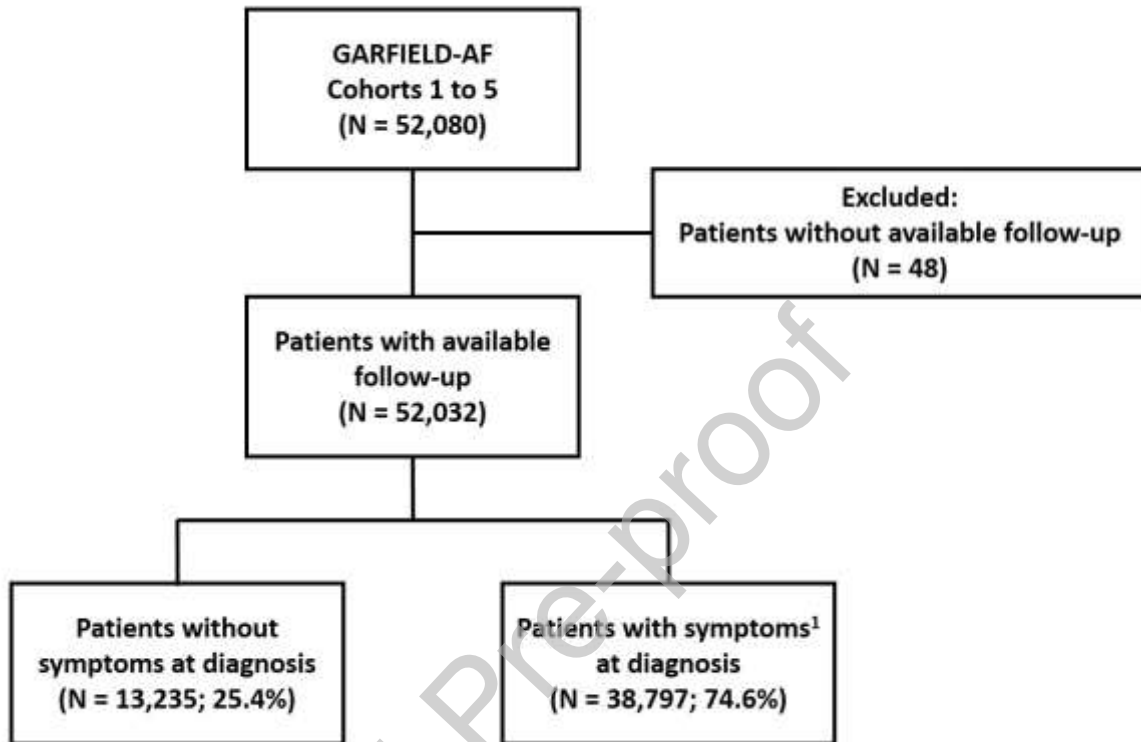
Figure 1. Flowchart for selection of study population.

[1]Palpitations, shortness of breath, chest pain/discomfort, dizziness, tiredness, sweating, fainting, other.

Figure 2. Antithrombotic therapy at inclusion following diagnosis in asymptomatic and symptomatic atrial fibrillation patients stratified by CHA$_2$DS$_2$-VASc score a) <2 or b) ≥2. AP, antiplatelet; NOAC, non-vitamin K antagonist oral anticoagulant; VKA, vitamin K antagonist.
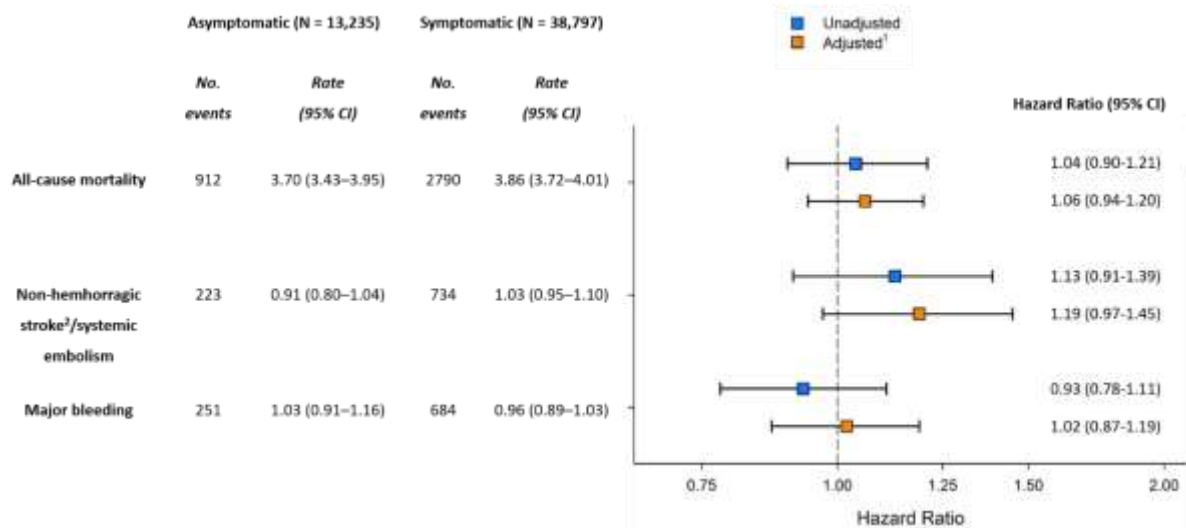
Figure 3. Hazard ratios (unadjusted and adjusted[1]) and corresponding 95% CIs for 2-year outcomes in patients with versus without (reference) symptoms at diagnosis. HR >1 indicated increased risk for symptomatic patients. [1]Adjusted for sex, age, diabetes, hypertension, congestive heart failure, vascular disease, prior stroke/transient ischaemic attack/systemic embolism, ethnicity, history of bleeding, moderate–severe chronic kidney disease, OAC treatment, smoking status, and alcohol consumption. [2]Combining ischemic and unknown stroke.
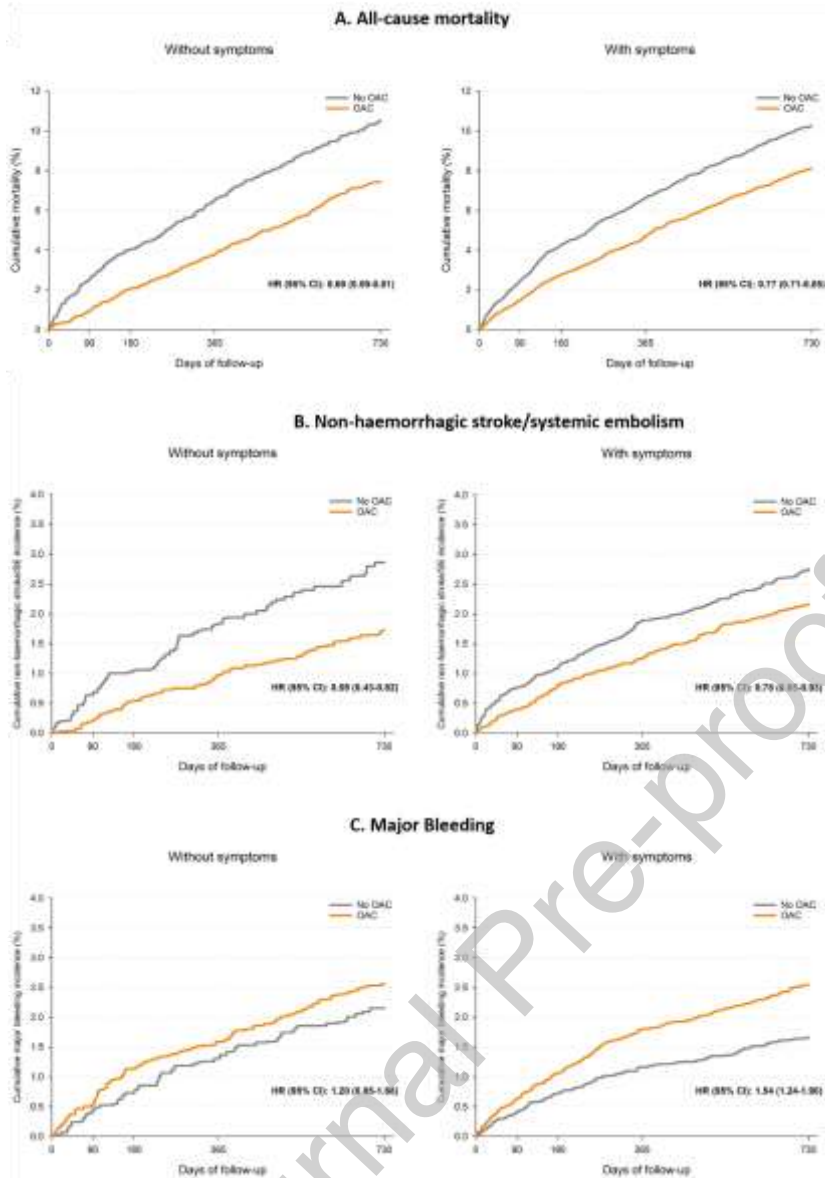
Figure 4. Adjusted[1] cumulative incidence rates for a) all-cause mortality, b) non-hemorrhagic stroke/systemic embolism, and c) major bleeding in patients with asymptomatic (left curves) and symptomatic (right curves) atrial fibrillation treated with OAC or no OAC over 2 years. [1]Adjusted for sex, age, diabetes, hypertension, congestive heart failure, vascular disease, prior stroke/transient ischaemic attack/systemic embolism, ethnicity, history of bleeding, moderate–severe chronic kidney disease, type of atrial fibrillation, OAC treatment, smoking status, and alcohol consumption.

Tables

Title: Clinical outcomes in asymptomatic and symptomatic atrial fibrillation patients in GARFIELD-AF: Implications for atrial fibrillation screening

Table 1. Baseline characteristics in asymptomatic and symptomatic patients with atrial fibrillation

Parameter	Asymptomatic (N = 13,235)	Symptomatic (N = 38,797)
Sex male, n (%)	8501 (64.2)	20,541 (52.9)
Age, median (IQR), years	72.0 (65.0–79.0)	70.0 (62.0–78.0)
Ethnicity, n (%)		
White	8176 (63.7)	23,829 (62.8)
Hispanic/Latino	603 (4.7)	2789 (7.4)
Asian	3866 (30.1)	10,416 (27.5)
Other	186 (1.4)	883 (2.3)
BMI, median (IQR), kg/m^2	26.6 (23.8–30.1)	27.0 (24.0–30.9)
SBP, median (IQR), mmHg	131.0 (120.0–144.0)	130.0 (120.0–145.0)
DBP, median (IQR), mmHg	80.0 (70.0–86.0)	80.0 (70.0–90.0)
Pulse rate, median (IQR), min^{-1}	80.0 (70.0–95.0)	86.0 (72.0–110.0)
Type of atrial fibrillation, n (%)		
Permanent	2176 (16.4)	4454 (11.5)
Persistent	2087 (15.8)	5671 (14.6)
Paroxysmal	3324 (25.1)	10,983 (28.3)
New onset (unclassified)	5643 (42.7)	17,688 (45.6)
Care setting location at diagnosis, n (%)		

Hospital	6748 (51.0)	23,593 (60.8)
Office	5740 (43.4)	9841 (25.4)
AC clinic	102 (0.8)	237 (0.6)
Emergency room	639 (4.8)	5125 (13.2)
Medical history, n (%)		
Heart failure	1786 (13.5)	9953 (25.7)
Acute coronary syndrome	1219 (9.2)	4317 (11.2)
Vascular disease[1]	2732 (20.8)	10,086 (26.2)
Prior stroke	1438 (10.9)	2440 (6.3)
Prior bleeding	372 (2.8)	944 (2.4)
Hypertension	9975 (75.6)	29,635 (76.6)
Hypercholesterolemia	5241 (40.6)	15,718 (41.9)
Diabetes	3037 (23.0)	8509 (21.9)
Moderate–severe chronic kidney disease	1411 (11.0)	3944 (10.5)
Treatment, n (%)		
NOAC ± AP	3906 (29.8)	10,217 (26.7)
VKA ± AP	5187 (39.6)	14,996 (39.3)
AP alone	2350 (17.9)	8411 (22.0)
None	1659 (12.7)	4581 (12.0)
CHA_2DS_2-VASc score, median (IQR)	3.0 (2.0–4.0)	3.0 (2.0–4.0)
HAS-BLED score, median (IQR)[2]	1.0 (1.0–2.0)	1.0 (1.0–2.0)

[1]Peripheral artery disease and/or coronary artery disease.

[2]"Labile INR" not collected at baseline; therefore, maximum score 8 (not 9).

AP, antiplatelet; BMI, body mass index; DBP, diastolic blood pressure; IQR, interquartile range;

NOAC, non-vitamin K antagonist oral anticoagulant; SBP, systolic blood pressure; VKA, vitamin K

antagonist.