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ORIGINAL ARTICLE

Characteristics and outcomes of atrial fibrillation patients with or without specific symptoms: results from the PREFER in AF registry

Ameet Bakhai[1]*, Harald Darius[2], Raffaele De Caterina[3], Angela Smart[4], Jean-Yves Le Heuzey[5], Richard John Schilling[6], José Luis Zamorano[7], Mit Shah[1], Peter Bramlage[8], and Paulus Kirchhof[9], on Behalf of the PREFER in AF Investigators

[1]Royal Free London NHS Trust, Barnet Hospital, London, UK; [2]Vivantes Clinics for Health, Berlin, Germany; [3]G. d'Annunzio University, Chieti-Pescara, Italy; [4]Daiichi Sankyo UK Ltd, Gerrards Cross, UK; [5]Georges Pompidou Hospital, René Descartes University, Paris, France; [6]Cardiology Department, Barts and The London School of Medicine and Dentistry, London, UK; [7]Department of Cardiology, Hospital Universitario Ramón y Cajal, Madrid, Spain; [8]Institut für Pharmakologie und Präventive Medizin, Mahlow, Germany; and [9]University of Birmingham, Institute of Cardiovascular Sciences and SWBH and UHB NHS trusts, Birmingham, UK

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Aims Atrial fibrillation (AF) is a common condition that is a major cause of stroke. A significant proportion of patients with AF are not classically symptomatic at diagnosis or soon after diagnosis. There is little information comparing their characteristics, treatment, and outcomes of patients with symptoms, which predominate in clinical trials to those without.

Methods and results We analysed data from the Prevention of Thromboembolic Events—European Registry in Atrial Fibrillation. This was a prospective, real-world registry with a 12-month follow-up that included AF patients aged 18 years and over. Patients were divided into those with and without AF symptoms using the European Heart Rhythm Association (EHRA) score (Category I vs. Categories II–IV). Of the 6196 patients (mean age 72 years) with EHRA scores available, 501 (8.1%) were asymptomatic. A lower proportion of asymptomatic patients was female (22.8 vs. 41.2%), with less noted to have heart failure and coronary artery disease ($P < 0.01$ for all). There were no differences in terms of the prevalence of diabetes, obesity, or prior stroke. Asymptomatic patients had a lower CHA_2DS_2-VASc score (2.9 ± 1.7 vs. 3.4 ± 1.8; $P < 0.01$) and HAS-BLED score (1.8 ± 1.1 vs. 2.1 ± 1.2; $P < 0.01$). During the 1-year follow-up, adverse events occurred at similar frequencies in asymptomatic and symptomatic patients (1.6 vs. 0.8% for ischaemic stroke; $P = 0.061$; 1.4 vs. 1.3% for transient ischaemic attack; $P = 0.840$). Patients with higher CHA_2DS_2-VASc and HAS-BLED scores experienced more events, independent of symptoms. Antithrombotic therapy was comparable for both groups at baseline and at follow-up.

Conclusions The similar clinical characteristics and frequency of adverse events between asymptomatic and symptomatic AF patients revives the question of whether screening programmes to detect people with asymptomatic AF are worthwhile, particularly in those aged 65 and over potentially likely to have clinical and economic benefits from anticoagulants. This evidence may be informative if clinicians may not be comfortable participating in future clinical trials, leaving asymptomatic patients with AF and high stroke risk without anticoagulation.

Keywords Atrial fibrillation • Silent AF • Asymptomatic AF • Stroke • Bleeding • Registry

Introduction

The prevalence of atrial fibrillation (AF) has been reported to be ~1.5–2%,[1] steadily increasing as a result of an aging population and increasing technologies able to detect AF, with the associated morbidity being responsible for a mounting burden on healthcare systems.[2–5] Previous studies of patients with AF have documented a five-fold greater risk of stroke, often as a result of atrial thrombus formation.[6] Additionally, AF has been shown to increase the risk of subsequent heart failure, dementia, and premature death.[1,6–9] In

* Corresponding author. Email: asbakhai@nhs.net

order to reduce the thromboembolic complication of stroke, anticoagulants are usually prescribed to patients aged 65 years or over who are diagnosed with AF, while antiplatelet monotherapy is much less effective.[1,6] Anticoagulation may be achieved using either a vitamin K antagonist (VKA) such as warfarin or a non-VKA (or 'novel') oral anticoagulant (NOAC).[10,11]

There are many symptoms that may herald the presence of AF, including palpitations, chest pain, exertional dyspnoea, lightheadedness, and syncope; however, a proportion of patients display no symptoms at diagnosis or short or shortly after diagnosis.[2,12,13] Asymptomatic, or silent, AF may be detected during admission for a stroke or heart failure, or during pre-operative assessment, evaluation of an unrelated medical condition, routine clinical or fitness examination, via automated blood pressure monitors, or via an epidemiological study.[13]

Opinion is divided on the use of national screening programmes for detecting AF, with European guidelines recommending opportunistic screening for patients aged 65 years or older,[14] while the American guidelines do not refer to any such programmes.[6] A recent report from the UK stated that there was likely a benefit to screening on a national level, but that it was uncertain whether this would be cost-effective.[15] This conclusion was drawn in large part due to the lack of involvement of asymptomatic AF patients instroke prevention studies with anticoagulation. The guidance suggested that the lack of this specific involvement may challenge the clinical assumptions of potential benefit in this subgroup of AF patients.

While there is a substantial body of literature regarding the prognosis and treatment of patients with symptomatically detected AF, there are currently inadequate data detailing the outcomes for asymptomatic patients.[16] The likely delay in diagnosis, and therefore treatment, of AF in this population could result in significant morbidity and mortality.[2,17] Furthermore, as there is often a focus on relieving symptoms when treating AF, it is possible that antithrombotic therapy and rate control agents are underused in this population.[2,18]

The Prevention of Thromboembolic Events—European Registry in Atrial Fibrillation (PREFER in AF) was designed to gain insight into the characteristics and management of patients with AF.[19] The present *post hoc* analysis compares data collected from asymptomatic and symptomatic AF patients in order to identify potential differences in cardiovascular outcomes and treatment.

Methods

Study design

Patients were consecutively enrolled in the PREFER in AF registry from January 2012 to January 2013 in 461 centres across seven European countries (Austria, France, Germany, Italy, Spain, Switzerland, and the UK).[19] This prospective observational study involved a baseline visit and a follow-up visit 1 year later.

All patients provided written informed consent, and the study was conducted in accordance with the Declaration of Helsinki and its amendments. Ethical approval was obtained according to the local regulations of each participating centre.

Patients

Patients were included if they were over 18 years of age and had a history of AF documented by electrocardiogram in the preceding 12 months. In order to minimize selection bias and to be more representative of a real-world situation, no exclusion criteria were set.

Patients were divided into two groups according to their European Heart Rhythm Association (EHRA) score.[20] This scoring method provides a simple clinical tool for assessing symptoms during AF, and only considers symptoms that are attributable to AF and reverse or reduce upon restoration of sinus rhythm or with effective rate control.[21] The groups were labelled as asymptomatic (EHRA I) or symptomatic (EHRA II–IV).

Documentation

Data were captured at each institution through completion of an electronic case report form (eCRF). A wide range of plausibility checks were carried out for the included variables. At baseline, patient characteristics, including demographics, type of AF, heart rhythm control, heart rate, left ventricular ejection fraction (LVEF), comorbidities, and pharmacotherapy, were documented. A CHA_2DS_2-VASc score and an HAS-BLED score were determined for each patient, indicating stroke and bleeding risk, respectively. At the 1-year follow-up visit, adverse events that had occurred during the 12-month period were documented. These included acute coronary syndrome (ACS), arterial embolism, ischaemic stroke, transient ischaemic attack, intracerebral bleeding, gastrointestinal bleeding, other life-threatening or major bleeding, venous thromboembolism, pulmonary thromboembolism, stent insertion, or coronary artery bypass grafting.

Estimates for death rates rely on spontaneous reporting instead of reporting of death as a specific event on its own. Data were extracted from the comments section of the eCRF and then verified with the relating sites to gain more information about the validity and further details. This makes death reporting potentially less accurate given that the diligence on adverse event reporting relies on investigator reporting.

Statistics

Descriptive analysis was carried out on available data. Categorical variables are presented as absolute values and percentages, with the statistical significance of differences between groups assessed by using a χ^2 test. Continuous variables are presented as means $\pm$ SD, with the statistical significance of differences between groups assessed using a *t*-test. A *P*-value of <0.05 was considered to be significant. For the comparison of outcomes at year between asymptomatic and symptomatic patients, odds ratios with 95% confidence intervals (CIs) were calculated by the logistic regression. Analysis was carried out using SAS (version 9.2).

Results

Patient characteristics

Of the 7245 patients initially enrolled, 6412 had follow-up information available and 6196 had an EHRA score at baseline available (analysis set, FAS). At study enrolment, a total of 501 patients (8.1%) were classified as asymptomatic (EHRA I; *Figure 1*). The remaining 5695 patients (91.9%) were classified as having mild symptoms (EHRA II; 37.9%), severe symptoms (EHRA III; 32.5%), or disabling symptoms (EHRA IV; 21.5%).[14,20] There was a significantly lower proportion of females in the asymptomatic group (22.8 vs. 41.2%; $P < 0.01$), and the mean body weight was slightly lower (82.1 ± 17.0 vs. 84.3 ± 19.5 kg; $P = 0.001$) in comparison to the symptomatic patients (*Table 1*). There was some difference in the proportions of patients in the two groups with different types of AF ($P = 0.002$). Permanent AF was the predominant form for

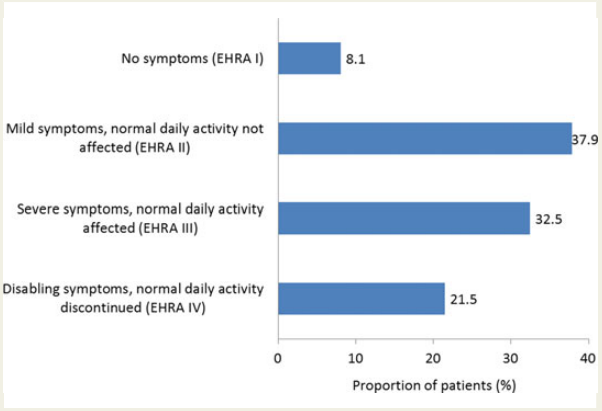

Figure 1 Classification of AF- related symptoms. AF, atrial fibrillation; EHRA, European Heart Rhythm Association.

both groups, with a higher percentage of asymptomatic patients diagnosed with this condition (45.8 vs. 38.7% for the symptomatic patients). Paroxysmal AF was found more frequently in the symptomatic group, while there were no great differences in the occurrence of persistent and long-standing persistent AF.

Asymptomatic patients had a slightly higher mean LVEF in comparison to the symptomatic cohort (59.4 ± 10.4% vs. 56.3 ± 11.6%; $P < 0.01$). While incidence of diabetes mellitus, obesity, and prior ischaemic stroke did not vary significantly between the two groups; hypertension, coronary artery disease (CAD), and heart failure were all less prevalent in the asymptomatic patients ($P < 0.01$ for all). Patients in the asymptomatic group had significantly lower mean CHA_2DS_2-VASc (2.9 ± 1.7 vs. 3.4 ± 1.8; $P < 0.01$) and HAS-BLED (1.8 ± 1.1 vs. 2.1 ± 1.2; $p < 0.01$) scores (*Table 1*).

In terms of treatment, a lower percentage of patients in the asymptomatic group received rhythm control therapy than those in the symptomatic group (52.5 vs. 68.3%; $P < 0.01$). On the other hand, the difference in the types of antithrombotic medication being taken by the patients in the two groups was not statistically significant ($P = 0.057$). Most patients were treated with a VKA, with smaller numbers taking an anti-platelet agent or an NOAC.

Outcomes at 1-year follow-up

Event rates of ischaemic stroke (1.6 vs. 0.8%; $P = 0.061$) and transient ischaemic attack (1.4 vs. 1.3%; $P = 0.840$; *Table 2*) were similar for the asymptomatic and symptomatic groups. There were 197 deaths recorded from baseline throughout the 1-year follow-up, captured via spontaneous reports (see Methods).

Of the asymptomatic patients (EHRA I), 5.0% experienced a cardiovascular event during the follow-up period (*Figure 2A*). While events rates were similar for patients with mild symptoms (EHRA II) at 4.5%, the rates for cohorts with severe (EHRA III) or disabling (EHRA IV) symptoms were significantly higher than compared with the asymptomatic group at 6.9% ($P = 0.1154$) and 9.8% ($P = 0.0013$), respectively. There was a general trend towards more patients with higher CHA_2DS_2-VASc scores experiencing an event during the 12 months ($P = 0.0070$ for asymptomatic patients; $P < 0.0001$ for symptomatic patients; *Figure 2B*); when the patients were divided according to HAS-BLED score, there was also a trend towards more patients with a higher risk experiencing an event ($P = 0.0481$ for asymptomatic patients; $P < 0.0001$ for symptomatic patients; *Figure 2C*). For patients with a score of 4–9, a lower proportion of asymptomatic patients reported an event (8.0 vs. 15.8%; $P = 0.29$).

For both the asymptomatic and symptomatic AF patients, there was an increase in the proportions of patients receiving no antithrombotic therapy from baseline to the 1-year follow-up visit. This reflected the decrease in anti-platelet agents and VKAs, which exceeded the observed increase in the use of NOACs (*Figure 3*). VKAs were the most commonly prescribed agents for both patient groups at baseline and at follow-up during the recruitment and follow-up years from 2012.

Discussion

Hypothesis testing research into the role of anticoagulation in asymptomatic patients is evidently not possible. Neither an ethics board nor the majority of key physicians (mostly cardiologists and stroke specialists) would be comfortable withholding anticoagulation from patients with AF at high risk of stroke. In this setting, there is need for observational data into this matter, documenting patients with AF that may or may not have symptoms related to AF. As many such AF patients are prescribed anticoagulation by their clinicians, it may not be possible to observe unbiased event rates in asymptomatic AF patients. It was therefore our aim to describe patient characteristics, treatment and outcomes in asymptomatic versus symptomatic patients with AF which led to the conclusion that risk profile and outcomes of these patients in no different.

A lower proportion of asymptomatic patients were found to have paroxysmal AF, in agreement with other studies, which may be a reflection of the transient nature of the condition causing difficulties for its diagnosis in the absence of symptoms.[17,22,23]

It is well established that heart failure and AF are closely linked, with common pathophysiological mechanisms, risk factors, and symptoms.[24] This similarity of symptoms may explain why a higher proportion of symptomatic AF patients additionally had heart failure, in comparison to patients with no symptoms. Flaker *et al.* reported comparable results with those found in our study, while Boriani *et al.* documented much higher prevalence of heart failure in their AF patients, with a slightly higher frequency in those with symptoms.[17,18] The reason behind this discrepancy is unclear, although the asymptomatic patients in this latter study had a higher prevalence of some co-morbidities and higher CHA_2DS_2-VASc and HAS-BLED scores that those with symptoms, in contrast to the findings of both the present study and that of Flaker *et al.*

Antithrombotic therapy did not vary greatly between the two groups at either baseline or follow-up, with the majority of patients taking VKAs. Only low proportions were not treated with any such therapy, reflecting good adherence to European guidelines.[14] These data indicate that pharmacological treatment of asymptomatic patients was similar to that of those that were symptomatic. On the other hand, a higher proportion of symptomatic patients were treated with a rhythm control strategy, which may be due to physicians prescribing such therapy based on symptoms rather than AF diagnosis.

Table 1 Patient characteristics ($n = 6196$)

	Asymptomatic patients mean ± SD or *n*/*N* (%) ($n = 501$)	Symptomatic patients mean ± SD or *n*/*N* (%) ($n = 5695$)	*P*-value
Age (years)[a]	71.5 ± 9.3	71.8 ± 10.4	0.522
Female gender	114/501 (22.8)	2345/5692 (41.2)	<0.01
Bodyweight (kg)[b]	82.1 ± 17.0	84.3 ± 19.5	0.001
AF type			
Paroxysmal	112/498 (22.5)	1714/5686 (30.1)	0.002
Persistent	123/498 (24.7)	1352/5686 (23.8)	
Long-standing persistent	35/498 (7.0)	421/5686 (7.4)	
Permanent	228/498 (45.8)	2199/5686 (38.7)	
LVEF (%)[c]	59.4 ± 10.4	56.3 ± 11.6	<0.01
Comorbidities			
Diabetes mellitus	101/500 (20.2)	1267/5693 (22.3)	0.288
Hypertension	339/500 (67.8)	4175/5694 (73.3)	0.008
Obesity	140/498 (28.1)	1576/5687 (27.7)	0.848
CAD	80/501 (16.0)	1387/5689 (24.4)	<0.01
Prior ischaemic stroke	44/501 (8.8)	494/5691 (8.7)	0.938
Heart failure	44/501 (8.8)	1290/5688 (22.7)	<0.01
CHA_2DS_2-VASc score[d]	2.9 ± 1.7	3.4 ± 1.8	<0.01
HAS-BLED score[e]	1.8 ± 1.1	2.1 ± 1.2	<0.01
Rhythm control strategy	263/501 (52.5)	3886/5691 (68.3)	<0.01
Anti-arrhythmic drugs (%)			
Amiodarone (%)	72/501 (14.4)	1417/5695 (24.9)	<0.0001
Dronedarone (%)	11/501 (2.2)	230/5695 (4.0)	0.0408
Flecainide (%)	27/501 (5.4)	596/5695 (10.5)	0.0003
Propafenone (%)	8/501 (1.6)	178/5695 (3.1)	0.0545
Sotalol (%)	28/501 (5.6)	318/5695 (5.6)	0.9963
Quinidine (%)	1/501 (0.2)	11/5695 (0.2)	0.9749
Others (%)	107/501 (21.4)	1695/5695 (29.8)	<0.0001
Antithrombotic therapy			
Anti-platelet agent (AP)	55/501 (11.0)	634/5695 (11.1)	0.057
VKA	359/501 (71.7)	3781/5695 (66.4)	
AP plus VKA	33/501 (6.6)	585/5695 (10.3)	
Novel oral anticoagulant	26/501 (5.2)	359/5695 (6.3)	
None	28/501 (5.6)	336/5695 (5.9)	

AF, atrial fibrillation; LVEF, left ventricular ejection fraction; CAD, coronary artery disease; ACS, acute coronary syndrome; VKA, vitamin K antagonist.
[a]$N = 501$ (asymptomatic), $N = 5695$ (symptomatic).
[b]$N = 484$ (asymptomatic), $N = 5608$ (symptomatic).
[c]$N = 360$ (asymptomatic), $N = 4635$ (symptomatic).
[d]$N = 477$ (asymptomatic), $N = 5277$ (symptomatic).
[e]$N = 423$ (asymptomatic), $N = 4769$ (symptomatic).

We found that a significantly lower proportion of asymptomatic patients were female in comparison to those that were symptomatic and it is tempting to speculate that they are more sensitive to symptoms, but it is more likely that this is reflective of the gender bias in research participation. Similar values to these were reported by Flaker *et al.* for the cohort of AF patients in the AFFIRM study (33 and 41% female asymptomatic and symptomatic patients, respectively), while other studies have also described a lower percentage of female asymptomatic patients.[17,18,22] This may have implications for proposed systematic screening programmes, which have so far demonstrated poor cost-effectiveness.[25] Older age has also been reported to be predictive of asymptomatic AF; however, in the present study, we detected no significant difference in the mean age of the two groups.[17]

At the 1-year follow-up visit, there were few differences evident in terms of the proportions of patients in each group that had experienced an adverse event since baseline. Rates of bleeding events and stroke were found to be low in both groups. The higher incidence of ischaemic stroke documented for the asymptomatic group almost reached statistical significance (*Table 2*).

Table 2 Patient outcomes at 1 year

	Asymptomatic patients, *n*/*N* (%)	Symptomatic patients, *n*/*N* (%)	OR (95% CI)	*P*-value
Strokes				
Ischaemic stroke	8/489 (1.6)	44/5514 (0.8)	0.48 (0.23–1.03)	0.061
Transient ischaemic attack	7/488 (1.4)	73/5510 (1.3)	0.92 (0.42–2.02)	0.840
Haemorrhagic stroke	2/488 (0.4)	15/5512 (0.3)	0.66 (0.15–2.91)	0.586
Arterial embolism	2/488 (0.4)	11/5514 (0.2)	0.49 (0.11–2.20)	0.3481
Bleeding events				
Gastrointestinal bleeding	4/488 (0.8)	83/5517 (1.5)	1.85 (0.68–5.06)	0.232
Other life-threatening or major bleeding	5/488 (1.0)	65/5513 (1.2)	1.15 (0.46–2.88)	0.761

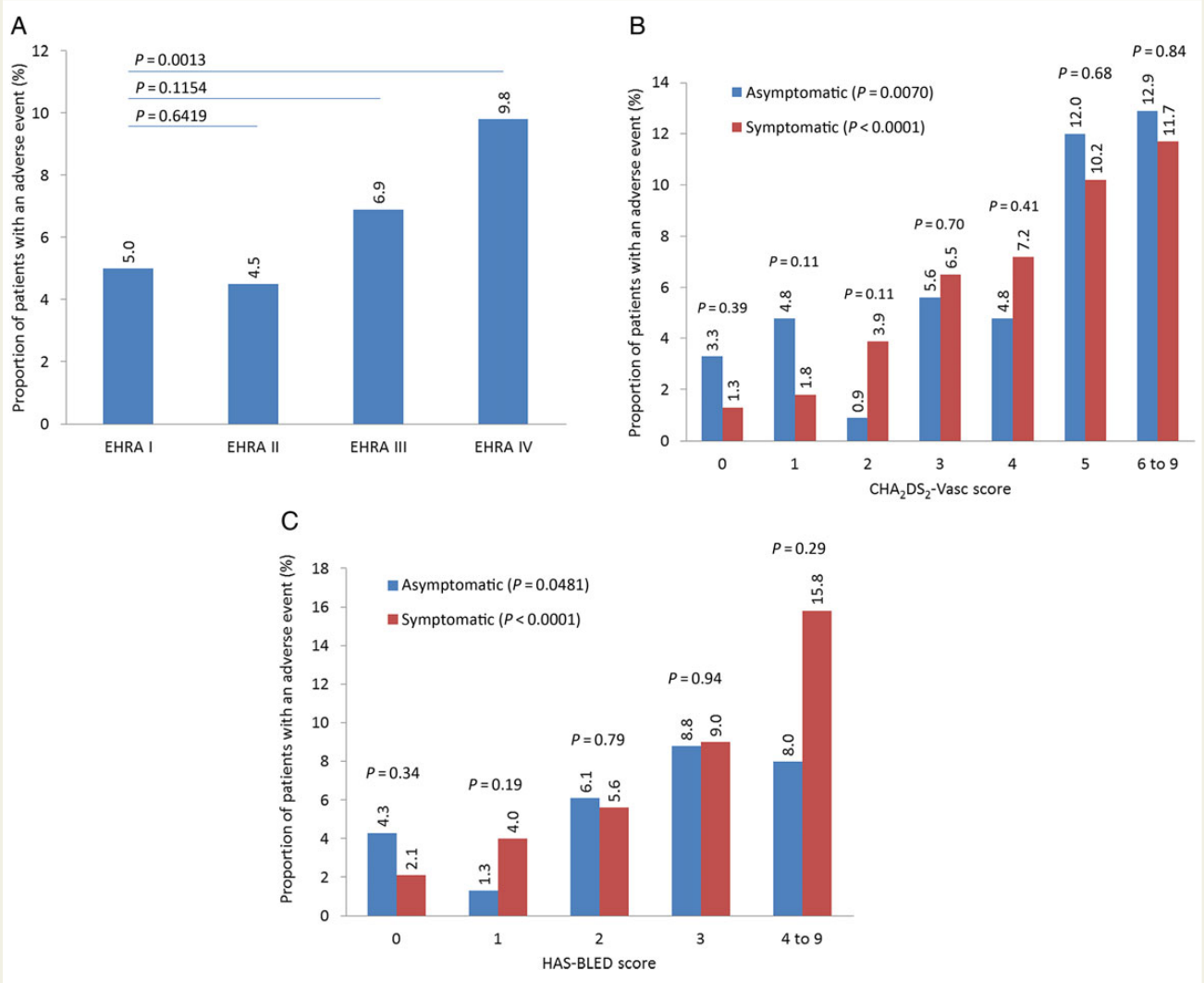

Figure 2 Proportions of patients experiencing an event during the 12 months after the baseline visit. (*A*) occurrence of events according the EHRA score [20]; p-values were derived from logistic regression analysis; (*B*) occurrence of events according to CHA_2DS_2-VASc score; p-values were determined using Cochran Armitage test; (*C*) occurrence of events according to HAS-BLED score. Events include acute coronary syndrome, myocardial infarction, arterial embolism, decompensated heart failure, any stroke, syncope, transient ischemic attack, and ventricular arrhythmia. EHRA, European Heart Rhythm Association score: EHRA I, no symptoms; EHRA I, mild symptoms, normal daily activity not affected; EHRA III, severe symptoms, normal daily activity affected; EHRA IV, disabling symptoms, normal daily activity discontinued. CHA_2DS_2-VASc score is the estimated risk of stroke in patients with AF; HAS-BLED score is the estimated 1-year risk of major bleeding in patients with AF. *P*-values were determined using Cochran Armitage test.

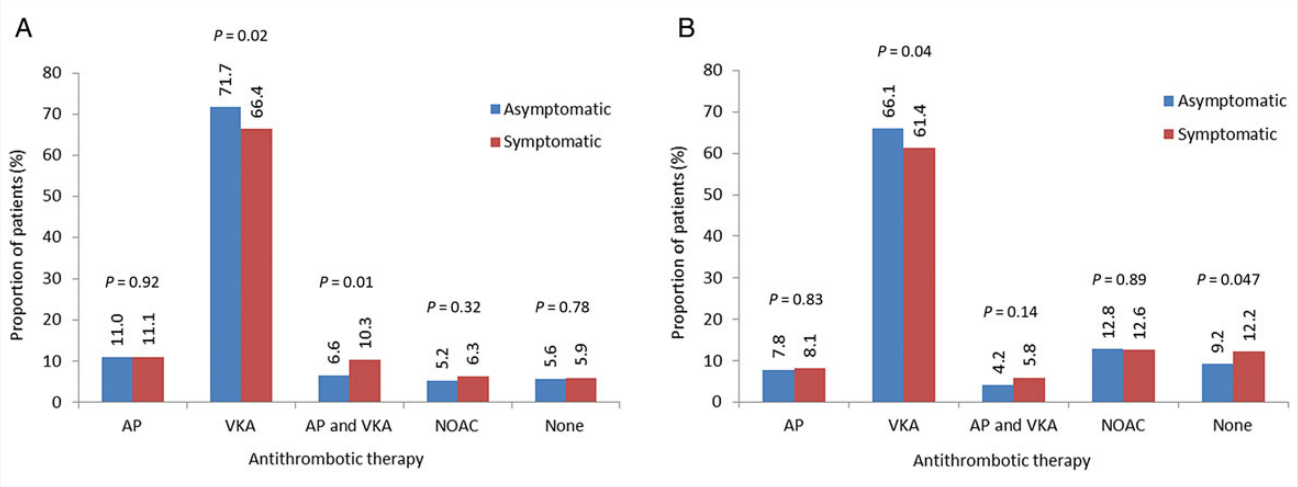

Figure 3 Antithrombotic therapy at baseline (*A*) and follow- up (*B*). AP, antiplated agent; VKA, vitamin K antagonist; NOAC, novel oral anticoagulant.

Incidence of combined events was highest for the patients with the most severe symptoms at baseline (EHRA IV), but there was little difference between patients with no (EHRA I) or mild (EHRA II) symptoms. When occurrence of events during follow-up was compared for patients with different CHA_2DS_2-VASc scores, it was found that those with the highest scores were more likely to experience an event, independent of the presence of symptoms. When stratified according to their HAS-BLED score, there was a general trend towards patients being more likely to experience an event if they had a higher score; however, the only significant difference was the poorer outcome for the symptomatic patients above a score of 4. Together, these data indicate that the occurrence of an adverse event during the 1-year follow-up period was mainly determined by the extent of co-morbid risk factors rather than the presence of AF symptoms at study enrolment. This highlights the importance of identifying AF in patients without symptoms in order to reduce the risk of thromboembolic complications and suggests that proposals for screening programmes should be revisited. Such strategies may involve targeting patients with risk factors, such as heart failure or prior myocardial infarction, or more extensive screening of members of the general population that are above a certain age.[25]

Limitations

A key limitation of the present study is that only asymptomatic patients that were diagnosed (and thus already considered for treatment) were captured, while PREFER in AF did not prospectively capture patients with undetected asymptomatic AF. We fully acknowledge this is a *post hoc* subgroup analysis undertaken for the purpose of exploring outcomes and treatment variations. For this reason, we did not carry out multivariate analysis. However, these data are retrieved from a large, robust, prospective registry to inform a data gap and to assist in decision-making to help the design of any future studies and economic models. Additionally, we note that patients were asymptomatic at registry entry and not necessarily at initial presentation, which may have been earlier than study entry. The overlap between AF and heart failure symptoms is likely to have introduced a bias into the analysis as, despite the use of EHRA guidelines, it is difficult to accurately attribute such symptoms to one condition or the other. A further limitation is that the asymptomatic subgroup was too small to allow robust comparisons between those appropriately on and off anti-thrombotic treatments for adverse events. The large number of patients for whom no follow-up information was available should also be taken into account. The missing values from the 1-year follow-up could therefore potentially introduce some bias; however, as an exploratory study, the information provides valuable insight into the characteristics of patients with asymptomatic AF.

Conclusion

In this large cohort of patients with AF in the PREFER-AF registry, we found that those without symptoms did not differ greatly from those with symptoms in terms of clinical characteristics. During the year-long follow-up, the occurrence of adverse events was similar for the two groups, but was higher for patients with greater morbidity at baseline, independent of the presence of symptoms. However, stroke rates in particular were comparable for patients with and without symptoms. This evidence may be informative if clinicians may not be comfortable participating in future clinical trials, leaving asymptomatic patients with AF and high stroke risk without anticoagulation.

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Conflict of interest: A.B. has received speaker and advisory board honoraria from multiple device and pharmaceutical partners, including Daiichi-Sankyo Europe GmbH, Bayer, and Boehringer Ingelheim. He is a director of Amore Health Ltd and works within the NHS (UK). He is R&D Deputy Director and consultant cardiologist at Royal Free London NHS Trust and participates in clinical trials sponsored by a variety of companies. H.D. Steering Committee member and National Coordinator for Germany RE-LY, APPRAISE-1 and 2, Garfield Registry, and PREFER in AF. Fees, honoraria, and research funding from AstraZeneca, Bayer, Berlin-Chemie, Boehringer Ingelheim, Boston Scientific, Bristol-Myers Squibb, Daiichi-Sankyo, Lilly, MSD Sharp&Dohme, BMFT, Harvard Med. Res. Inst., and Thrombosis Research Institute. R.D.C. Lecture fees and honoraria from Daiichi-Sankyo, Boehringer Ingelheim, Bayer, Bristol-Myers Squibb, Pfizer, and Lilly. J.-Y.L.H. Consultant/conferences/advisory board for Sanofi-Aventis, BMS/Pfizer, Meda, Boehringer Ingelheim, MSD, Bayer, Servier, and Daiichi-Sankyo A.S. Employee of Daiichi-Sankyo UK. J.L.Z. Speaker honoraria from Sanofi, Servier, and Daiichi-Sankyo. P.B. Consultancy fees and/or research funding from Bayer, Daiichi-Sankyo, Edwards Lifesciences, Harvest Technologies, Hexal, Merck, Pfizer, Novartis, Sanofi, Servier, Takeda, and UCB. R.J.S. Speaker honoraria, congress travel support and or research grants from Boeringher Ingelheim, Medtronic, Biosense Webster, St Jude Medical, Hansen Medical, Daiichi-Sankyo, Biotronik, and Boston Scientific. P.K. Consulting fees and honoraria from Boeringher Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, Johnson & Johnson, Medtronic, MSD, Pfizer, and Servier. Research Grants from Bristol-Myers Squibb/Pfizer, Cardiovascular Therapeutics, Daiichi-Sankyo, Sanofi, and St. Jude Medical.

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