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CLINICAL RESEARCH

Asymptomatic atrial fibrillation among hospitalized patients: clinical correlates and in-hospital outcomes in Improving Care for Cardiovascular Disease in China-Atrial Fibrillation

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Aims The clinical correlates and outcomes of asymptomatic atrial fibrillation (AF) in hospitalized patients are largely unknown. We aimed to investigate the clinical correlates and in-hospital outcomes of asymptomatic AF in hospitalized Chinese patients.

Methods and results We conducted a cross-sectional registry study of inpatients with AF enrolled in the Improving Care for Cardiovascular Disease in China-Atrial Fibrillation Project between February 2015 and December 2019. We investigated the clinical characteristics of asymptomatic AF and the association between the clinical correlates and the in-hospital outcomes of asymptomatic AF. Asymptomatic and symptomatic AF were defined according to the European Heart Rhythm Association score. Asymptomatic patients were more commonly males (56.3%) and had more comorbidities such as hypertension (57.4%), diabetes mellitus (18.6%), peripheral artery disease (PAD; 2.3%), coronary artery disease (55.5%), previous history of stroke/transient ischaemic attack (TIA; 17.9%), and myocardial infarction (MI; 5.4%); however, they had less prevalent heart failure (9.6%) or left ventricular ejection fractions ≤40% (7.3%). Asymptomatic patients were more often hospitalized with a non-AF diagnosis as the main diagnosis and were more commonly first diagnosed with AF (23.9%) and long-standing persistent/permanent AF (17.0%). The independent determinants of asymptomatic presentation were male sex, long-standing persistent AF/permanent AF, previous history of stroke/TIA, MI, PAD, and previous treatment with anti-platelet drugs. The incidence of in-hospital clinical events such as all-cause death, ischaemic stroke/TIA, and acute coronary syndrome (ACS) was higher in asymptomatic patients than in symptomatic patients, and asymptomatic clinical status was an independent risk factor for in-hospital all-cause death, ischaemic stroke/TIA, and ACS.

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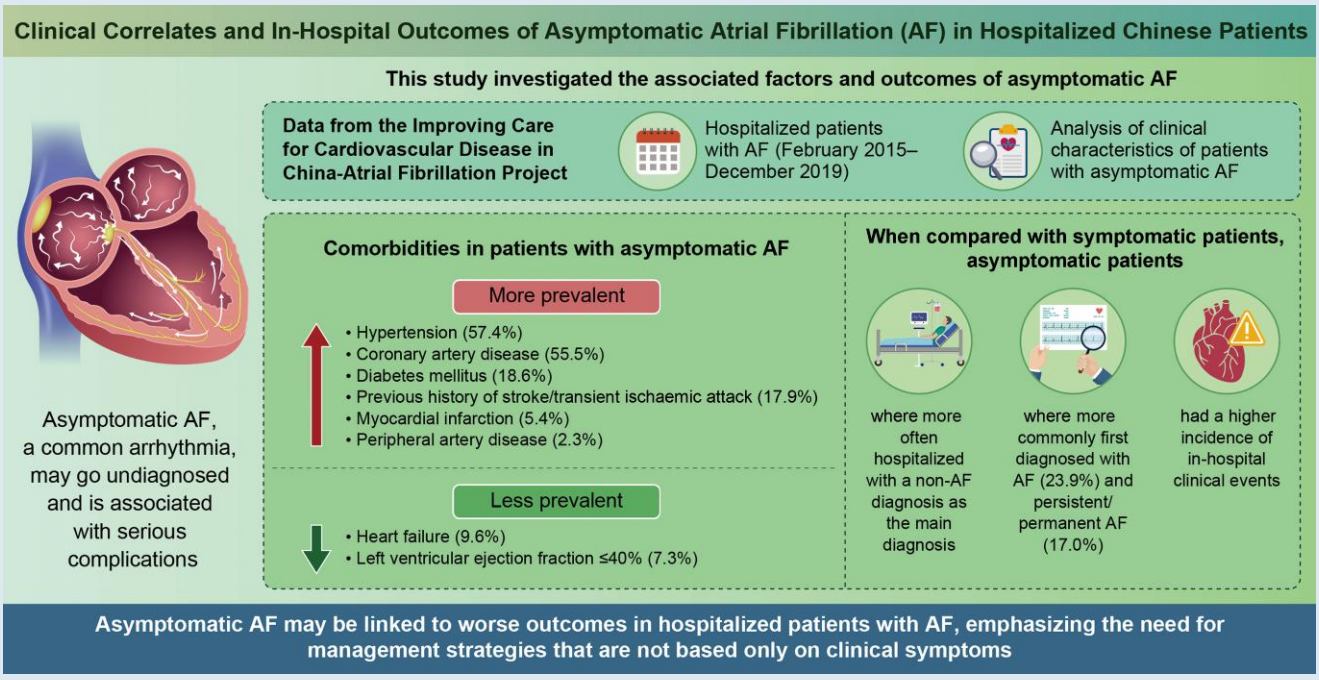
Conclusion Asymptomatic AF is common among hospitalized patients with AF. Asymptomatic clinical status is associated with male sex, comorbidities, and a higher risk of in-hospital outcomes. The adoption of effective management strategies for patients with AF should not be solely based on clinical symptoms.

Graphical Abstract



Keywords Atrial fibrillation • Acute coronary syndrome • Hypertension • Stroke

What's new?

- The clinical correlates and outcomes of asymptomatic atrial fibrillation (AF) in hospitalized patients are largely unknown.
- We aimed to investigate the clinical correlates and the in-hospital outcomes of asymptomatic AF in hospitalized Chinese patients.
- The adoption of effective management strategies for patients with AF should not be solely based on clinical symptoms.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice and a major public health concern, with an increasing rate of incidence and prevalence worldwide.[1] The main clinical AF symptoms are palpitations, fatigue, breathing difficulties, and decreased activity tolerance, necessitating medical treatment.[2,3]

Atrial fibrillation is usually diagnosed based on the occurrence of symptoms; however, asymptomatic patients with AF are often underdiagnosed and may become accustomed to their symptoms and delay medical treatment, leading to serious complications.[3–5] In the past, asymptomatic AF has received insufficient attention. However, some recent studies have revealed that asymptomatic AF is common in 'real-world' clinical practice. Symptomatic and asymptomatic AF occur in 60 and 40% of patients, respectively.[6] Meanwhile, asymptomatic AF is associated with a poor prognosis. Studies have shown that all-cause death and stroke are twice as common in patients with asymptomatic AF as in symptomatic AF.[4,6–10]

Data on the clinical characteristics of Asian patients with asymptomatic AF, particularly those from China, are limited. Additionally, the relationship between symptom presentation and clinical outcomes has not been consistent across studies and therefore remains controversial. We addressed this question in the Improving Cardiovascular Care in China-Atrial Fibrillation (CCC-AF) Project, the largest Chinese AF registry.[11] In this study, we aimed to report the following: (i) epidemiological data on asymptomatic AF in Chinese hospitalized patients; (ii) characteristics of patients with asymptomatic AF; and (iii) the associations between asymptomatic AF and in-hospital clinical outcomes.

Methods

Data collection

The methods and baseline data from the CCC-AF project, a national registry to improve AF management, have been reported.[11] Improving Cardiovascular Care in China-Atrial Fibrillation was launched in February 2015 as a cooperative project between the Chinese Society of Cardiology and the American Heart Association (AHA). The first 10–20 hospitalized patients with AF were enrolled sequentially at each hospital. Atrial fibrillation was included in the studies based on electrocardiograph (ECG) results recorded using a 12-lead ECG, a 24 h Holter, or other rhythm monitors. Patients with AF secondary to

reversible diseases, such as untreated thyroid disease and pulmonary embolism, were excluded.[11]

Between February 2015 and December 2019, 61 136 admitted patients with AF from 236 hospitals participated in the CCC-AF Project. We excluded 8347 patients with a previous valvular AF diagnosis and 259 patients with moderate-to-severe mitral stenosis on cardiac ultrasonography. Finally, 52 530 patients with non-valvular AF were enrolled in this study.

Definitions

The data elements and definitions of each variable were in accordance with the American College of Cardiology/AHA recommendations for AF clinical data standards.[12]

In this registry, a simple symptom score, proposed by the European Heart Rhythm Association (EHRA), was applied to quantify AF-related symptoms and clearly distinguish asymptomatic patients from patients with variable degrees of impairment in daily activity.[2] According to the EHRA score, we divided patients with EHRA I into the asymptomatic group and those with EHRA II–IV into the symptomatic group for analyses. The estimated glomerular filtration rate (eGFR) was calculated using the equation developed by the Chronic Kidney Disease Epidemiology Collaboration.[13] Thrombotic diseases were defined as all arterial and venous thrombotic diseases other than acute coronary syndrome (ACS) and stroke, including pulmonary embolism.

Statistical analyses

Continuous variables were expressed as means and standard deviations (SDs) or interquartile ranges. Categorical variables were presented as numbers and percentages. Categorical variables were compared using the χ^2 test when appropriate; otherwise, Fisher's exact test was used. We conducted a multivariable analysis using logistic regression to investigate the independent determinants of asymptomatic clinical status. The covariates chosen to be included in the model were age, sex, race, hospital levels, AF types, medical insurance, medical history of smoking, drinking, hypertension, diabetes mellitus, stroke or transient ischaemic attack (TIA), peripheral artery disease (PAD), heart failure, coronary artery disease (CAD), previous major bleeding, myocardial infarction (MI), chronic obstructive pulmonary disease (COPD), and chronic renal disease, and prior treatment, including catheter ablation, surgical ablation, anti-arrhythmic drug (AAD) use, electric cardioversion, and concomitant anti-platelet drug use before admission. To determine the associations between asymptomatic AF and in-hospital clinical events, the covariates included in the multivariable regression analysis were asymptomatic AF status, age, sex, race, hospital levels, AF types, medical insurance, medical history of smoking, drinking, hypertension, diabetes mellitus, stroke or TIA, PAD, heart failure, CAD, previous major bleeding, MI, COPD, and chronic renal disease and prior treatment including catheter ablation, surgical ablation, AAD use, electric cardioversion, and concomitant anti-platelet drug use. Statistical significance was set at $P < 0.05$.

Results

A total of 52 530 patients with a mean age of 69.2 (SD 12.0) were included in this study; 29 597 men accounted for 56.3% of the total population. In addition, 10 887 (20.7%) patients with newly diagnosed AF, 21 386 (40.7%) with paroxysmal AF, 12 802 (24.4%) with persistent AF, and 7455 (14.2%) with long-term persistent or permanent AF were identified.

Characteristics of patients with asymptomatic and symptomatic atrial fibrillation

Based on the EHRA classification of AF symptoms, the total population was divided into symptomatic (EHRA II–IV) and asymptomatic (EHRA I) groups, comprising 48 025 and 4505 patients, respectively (*Table 1*). The clinical characteristics of patients with AF according to the EHRA classification are shown in Supplementary material online, *Table S1*.

Patients with asymptomatic AF tended to be male, smokers, have high-coverage health insurance, have a medical history of hypertension, diabetes, coronary heart disease (CHD), previous ischaemic stroke/TIA, PAD, major bleeding, COPD, MI, and anti-platelet drug use prior to hospital admission (all $P < 0.05$). Patients with symptomatic AF were more likely to have a medical history of heart failure and a lower left ventricular ejection fraction (LVEF). Also, they were more likely to receive AADs for ventricular rate control, radiofrequency ablation, electrical cardioversion, and surgical ablation procedures before hospital admission (all $P < 0.05$).

Asymptomatic patients had longer hospital stays than symptomatic patients with AF [mean 9.9 (SD 6.3) days vs. 9.4 (SD 5.7) days; $P < 0.001$]. No significant differences were observed between both groups in age, ethnicity, history of alcohol consumption, chronic kidney disease, heart rate, body mass index, blood pressure, eGFR, LVEF, left atrial end-diastolic diameter, total cholesterol, low-density lipoprotein cholesterol, and previous anti-coagulation ($P > 0.05$). Patients with asymptomatic AF had higher mean hypertension, abnormal kidney and liver function, stroke, bleeding, labile INR, elderly and drugs or alcohol (HAS-BLED) scores than those with symptomatic AF ($P < 0.001$); however, the mean CHA_2DS_2-VAS scores were similar between the two groups ($P > 0.05$).

Atrial fibrillation pattern and main diagnosis between asymptomatic and symptomatic atrial fibrillation

As shown in *Figure 1*, newly diagnosed and permanent AF were more common in asymptomatic patients ($P < 0.001$), whereas paroxysmal AF was more prevalent in symptomatic patients with AF ($P < 0.001$). The distribution of persistent AF was similar between the two groups ($P < 0.001$).

With regard to the main diagnosis, AF was diagnosed at discharge in 35.7% of patients with asymptomatic AF ($P < 0.001$). Among those with non-AF as the main diagnosis, heart failure was the primary diagnosis in 15.6% of those with symptomatic AF and 12.6% of those with asymptomatic AF. The proportions of CAD, ischaemic stroke/TIA, thromboembolic disease, and other diseases between the asymptomatic and the symptomatic AF groups were 30.3 and 20.5, 3.2 and 0.6, 0.4 and 0.1, and 17.8 and 11.3%, respectively (*Figure 2*).

Multivariable analysis

Based on the multivariable logistic regression analysis, males [adjusted odds ratio (aOR): 1.40, 95% credibility interval (CI): 1.32–1.50], long-standing persistent or permanent AF (aOR: 1.11, 95% CI: 1.00–1.23), a previous ischaemic stroke or TIA (aOR: 1.38, 95% CI: 1.27–1.50), PAD (aOR: 1.36, 95% CI: 1.11–1.68), major bleeding (aOR: 1.25, 95% CI: 1.00–1.56), MI history (aOR: 1.25, 95% CI: 1.09–1.44), and prior concomitant treatment with anti-platelet drugs (aOR: 1.18, 95% CI: 1.05–1.31) were significantly associated with asymptomatic status after adjusting for several covariates (*Table 2*).

In-hospital outcomes associated with asymptomatic atrial fibrillation

The in-hospital clinical events in the entire population are presented in *Table 3*. In-hospital deaths occurred in 237 (0.5%) patients: 33 (0.7%) with asymptomatic AF and 204 (0.4%) with symptomatic AF. Overall, 400 (0.8%) patients were newly diagnosed with ischaemic stroke or TIA, including 53 (1.2%) with asymptomatic AF and 347 (0.7%) with symptomatic AF. Furthermore, 203 (0.4%) patients had newly diagnosed ACS, including 31 (0.7%) with asymptomatic AF and 172 (0.4%) with symptomatic AF. Also, 4436 (8.5%) patients experienced heart failure during the in-hospital period; 294 (6.5%) with asymptomatic AF and 4142 (8.6%) with symptomatic AF.

Table 1 Characteristics of patients with asymptomatic and symptomatic AF

Characteristics	Asymptomatic ($n = 4505$)	Symptomatic ($n = 48\,025$)	Total population	*P*-value
Age, years, mean (SD)	69.5 (12.1)	69.2 (12.0)	69.2 (12.0)	0.353
Age, years, *n* (%)				0.335
≤64	1455 (32.3)	15 617 (32.5)	17 072 (32.5)	
65–74	1337 (29.7)	14 648 (30.5)	15 985 (30.4)	
≥75	1713 (38.0)	17 760 (37.0)	19 473 (37.1)	
Length of stay (SD)	9.90 (6.3)	9.41 (5.7)	9.45 (5.7)	<0.001
Male, *n* (%)	2872 (63.8)	26 725 (55.6)	29 597 (56.3)	<0.001
Han nationality, *n* (%)	4403 (97.7)	46 782 (97.4)	51 185 (97.4)	0.188
Tertiary hospitals, *n* (%)	3640 (80.8)	41 324 (86.0)	44 964 (85.6)	<0.001
Medical insurance, *n* (%)				<0.001
High cover	2974 (66.0)	29 985 (62.4)	32 959 (62.7)	
Moderate cover	831 (18.4)	9321 (19.4)	10 152 (19.3)	
Low cover	700 (15.5)	8719 (18.2)	9419 (17.9)	
Medical history, *n* (%)				
Drinking	570 (12.7)	5814 (12.1)	6384 (12.2)	0.283
Smoking	1079 (24.0)	9992 (20.8)	11 071 (21.1)	<0.001
Hypertension	2586 (57.4)	26 674 (55.5)	29 260 (55.7)	0.016
Diabetes mellitus	837 (18.6)	8248 (17.2)	9085 (17.3)	0.017
CAD	2502 (55.5)	11 902 (24.8)	14 404 (27.4)	<0.001
Stroke or TIA	805 (17.9)	6303 (13.1)	7108 (13.5)	<0.001
PAD	104 (2.3)	744 (1.5)	848 (1.6)	<0.001
Heart failure	431 (9.6)	5681 (11.8)	6112 (11.6)	<0.001
Major bleed	92 (2.0)	714 (1.5)	806 (1.5)	0.004
COPD	238 (5.3)	2169 (4.5)	2407 (4.6)	0.019
Prior MI	245 (5.4)	1959 (4.1)	2204 (4.2)	<0.001
Chronic kidney disease	102 (2.3)	1125 (2.3)	1227 (2.3)	0.739
Heart rate, b.p.m. (SD)	85.3 (23.3)	88.7 (26.0)	88.4 (25.8)	<0.001
BMI, kg/m^2 (SD)	24.5 (3.7)	24.5 (3.85)	24.5 (3.8)	0.040
Blood pressure, median (SD)				
SBP, mmHg	79.0 (13.9)	79.6 (13.8)	79.6 (13.8)	0.446
DBP, mmHg	131.9 (21.7)	131.2 (20.9)	131.3 (21.0)	0.001
eGFR, mL/min/1.73 m^2 (SD)	89.7 (47.5)	90.9 (50.6)	90.8 (50.3)	0.135
Left atrial diameter, mm (SD)	41.8 (8.1)	41.6 (7.9)	41.7 (8.0)	0.689
LVEF, % (SD)	57.7 (11.1)	57.2 (11.4)	57.2 (11.4)	0.010
LVEF ≤ 40%, *n* (%)	330 (7.3)	4216 (8.8)	4546 (8.7)	0.001
Total cholesterol, mmol/L	4.0 (1.4)	4.1 (2.1)	4.1 (2.0)	0.002
LDL-cholesterol, mmol/L	2.4 (0.9)	2.3 (0.9)	2.3 (0.9)	0.951
CHA_2DS_2-VASc score, median (SD)	3.1 (1.8)	3.1 (1.7)	3.1 (1.7)	0.067
HAS-BLED risk score, median (SD)	1.3 (0.9)	1.2 (0.9)	1.3 (0.9)	<0.001
AF type, *n* (%)				<0.001
First diagnosed	1076 (23.9)	9811 (20.4)	10 887 (20.7)	
Paroxysmal	1564 (34.7)	19 822 (41.3)	21 386 (40.7)	
Persistent	1098 (24.4)	11 704 (24.4)	12 802 (24.4)	
Long-standing persistent/permanent	767 (17.0)	6688 (13.9)	7455 (14.2)	
Prior treatment, *n* (%)				
Prior concomitant with anti-platelet	416 (9.2)	3561 (7.4)	3977 (7.6)	<0.001
Prior treatment with anti-coagulant	719 (16.0)	8144 (17.0)	8863 (16.9)	0.087

Continued

Table 1 *Continued*

Characteristics	Asymptomatic ($n = 4505$)	Symptomatic ($n = 48\,025$)	Total population	*P*-value
Prior anti-arrhythmic drugs	263 (5.8)	4464 (9.3)	4727 (9.0)	<0.001
Prior catheter ablation	120 (2.7)	1755 (3.7)	1875 (3.6)	0.001
Prior electric cardioversion	37 (0.8)	693 (1.4)	730 (1.4)	0.001
Prior surgical ablation	11 (0.2)	109 (0.2)	120 (0.2)	0.817

AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PAD, peripheral artery disease; SBP, systolic blood pressure; TIA, transient ischaemic attack.

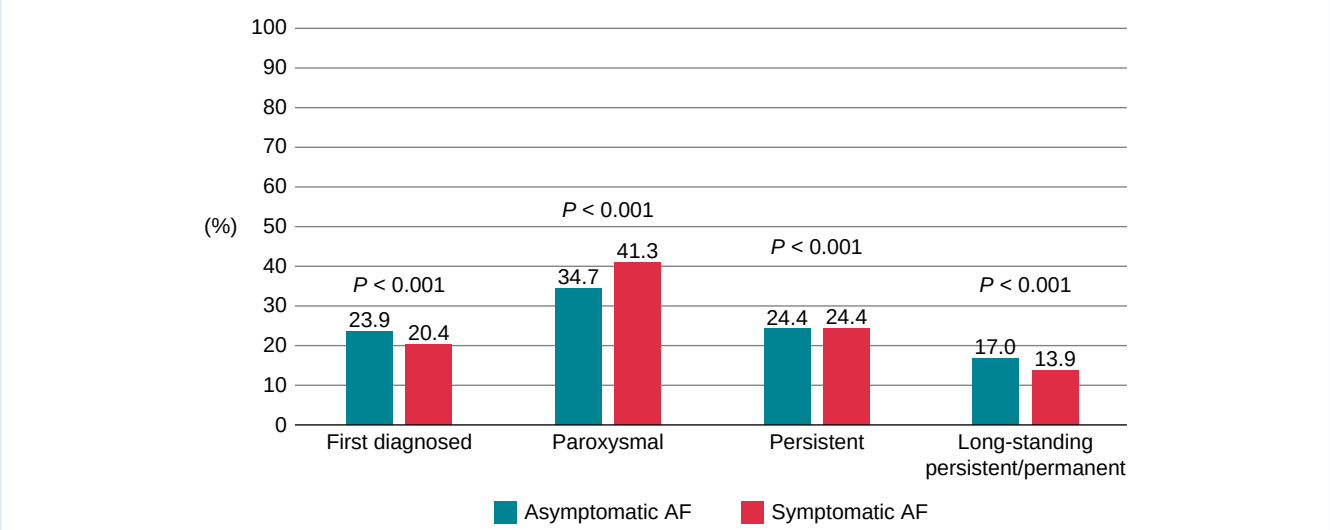


Figure 1 Distribution of asymptomatic AF and symptomatic AF in different AF patterns. AF, atrial fibrillation.

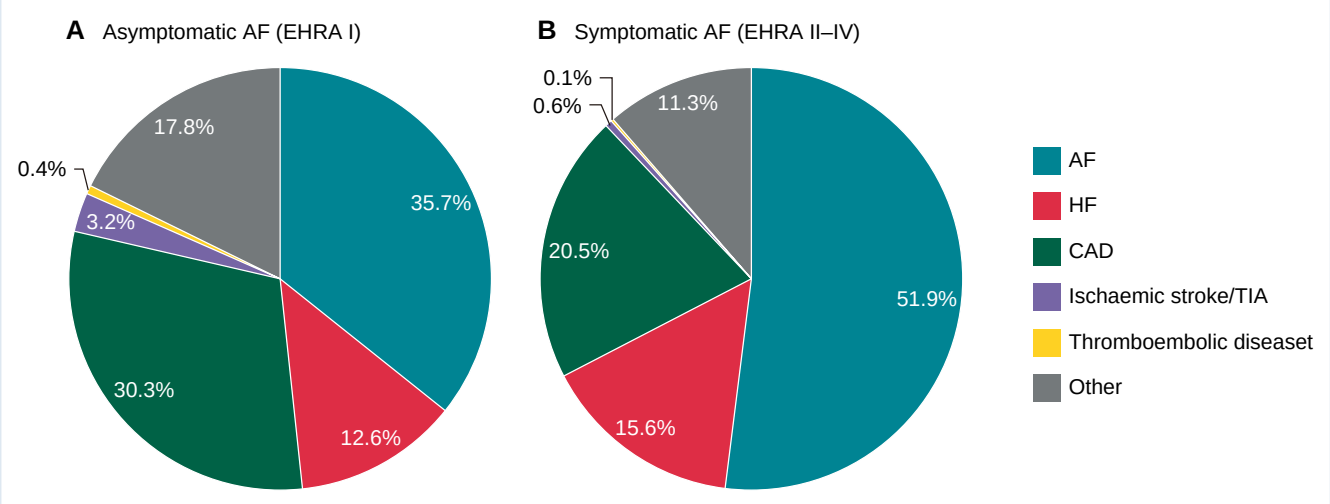


Figure 2 Distribution of the primary diagnosis in patients with asymptomatic AF (*A*) and symptomatic AF (*B*). AF, atrial fibrillation; CAD, coronary artery disease; EHRA, European Heart Rhythm Association; HF, heart failure; TIA, transient ischaemic attack.

As shown in *Table 3*, after adjusting for confounders, asymptomatic status was an independent risk factor for in-hospital all-cause death (aOR: 1.47, 95% CI: 1.00–2.14; $P < 0.05$), ischaemic stroke or TIA (aOR: 1.43, 95% CI: 1.06–1.91; $P < 0.05$), and ACS (aOR: 1.51, 95% CI: 1.02–2.22; $P < 0.05$). In the sensitivity multivariable analysis, the included covariates were asymptomatic AF/asymptomatic AF, age, sex, in-hospital anti-coagulant medication, congestive heart failure, hypertension, age, diabetes mellitus, stroke, vascular disease, age and sex (CHA_2DS_2-VASc) scores, admitted departments, HAS-BLED risk scores, and AF phenotype. Consistent with the results of the above multivariable analysis, asymptomatic status was a common factor for in-hospital all-cause death (aOR: 1.52, 95% CI: 1.05–2.20; $P < 0.05$), ischaemic stroke or TIA (aOR: 1.44, 95% CI: 1.07–1.93; $P < 0.05$), and ACS (aOR: 1.70, 95% CI: 1.15–2.51; $P < 0.05$) independent risk factors (*Table 3*).

Table 2 Multivariable analysis of factors associated with asymptomatic AF in the AF population

Variables	Adjusted OR (95% CI)	*P*-value
Male	1.40 (1.32–1.50)	<0.001
LVEF ≤40%	0.78 (0.70–0.88)	<0.001
Medical insurance		
High cover	Reference	
Moderate cover	0.92 (0.85–1.00)	0.056
Low cover	0.821 (0.75–0.90)	<0.001
AF type		
Newly diagnosed	Reference	
Paroxysmal	0.71 (0.65–0.77)	<0.001
Persistent	0.90 (0.82–0.98)	0.018
Long-standing persistent/permanent	1.11 (1.00–1.23)	0.038
Medical history		
Stroke or TIA	1.38 (1.27–1.50)	<0.001
PAD	1.36 (1.11–1.68)	0.004
Heart failure	0.73 (0.65–0.81)	<0.001
Previous bleeding	1.25 (1.00–1.56)	0.050
Prior MI	1.25 (1.09–1.44)	0.002
Prior treatment		
Prior concomitant with anti-platelet	1.18 (1.05–1.31)	0.004
Prior anti-arrhythmic drugs	0.64 (0.56–0.72)	<0.001
Prior electric cardioversion	0.66 (0.47–0.92)	0.015

The covariates included in the multivariable regression analysis were age, sex, race, hospital level, AF phenotype, medical insurance, medical history of smoking, drinking, hypertension, diabetes mellitus, stroke/TIA, PAD, heart failure, CAD, previous major bleeding, prior MI, COPD, chronic renal disease, and prior treatment, including catheter ablation, surgical ablation, AAD use, electric cardioversion, and concomitant anti-platelet drug use before admission.
AADs, anti-arrhythmic drug; AF, atrial fibrillation; CAD, coronary artery disease; CI, credibility interval; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; OR, odds ratio; PAD, peripheral artery disease; TIA, transient ischaemic attack.

Discussion

In this large national AF registry based on data obtained from hospitalized Chinese patients with AF, our principal findings are as follows: (i) among hospitalized patients with AF, asymptomatic patients accounted for 8.5%; (ii) asymptomatic patients were commonly males, those with more comorbidities such as hypertension, diabetes mellitus, PAD, CAD, previous history of stroke/TIA, and MI, but less commonly patients with heart failure or LVEF ≤40%; (iii) asymptomatic patients were commonly patients first diagnosed AF and long-standing persistent AF/permanent AF and were often admitted with non-AF diagnosis as the primary diagnosis; and (iv) the independent determinants of asymptomatic presentation were male sex, long-standing persistent AF/permanent AF, previous history of stroke/TIA, MI, PAD, and prior treatment with anti-platelet drugs. In-hospital clinical events, including all-cause death, ischaemic stroke/TIA, and ACS, were higher in asymptomatic patients than in symptomatic patients. An asymptomatic clinical status was an independent risk factor for these three in-hospital clinical events.

Although most patients with AF present with symptoms, ~15–50% of patients diagnosed with clinical AF are asymptomatic.[3,4,6,7] The frequency of asymptomatic AF varies widely and depends on the studied population, the temporal pattern of AF (paroxysmal, persistent, or permanent), and detection method. More sophisticated modes of detection and prolonged monitoring are more likely to aid AF detection.[14,15] In this study, we observed that the proportion of asymptomatic patients with AF is 8.5% of hospitalized patients with AF. This number is far lower than that reported in previous studies,[4,6,16,17] possibly because of our study population, which was comprised of hospitalized patients. Moreover, these patients usually have somatic, psychological, and other cardiovascular conditions that may be similar to AF symptoms or aggravate AF symptoms.

Consistent with previous studies, fewer women were asymptomatic in our study, possibly because women tended to seek care for a higher heart rate.[18–20] Patients with asymptomatic AF have fewer cardiac comorbidities.[20,21] However, in this study, we observed that asymptomatic AF was more common in patients with hypertension, diabetes, CHD, and previous MI. It is not completely clear why AF is more asymptomatic in people with these disease conditions; however, these patients may have a common epigenetic trait that is responsible for lower AF perception.[22,23] Rhythm control strategies, including AAD use, catheter ablation, and electric cardioversion, are more commonly used in patients with symptomatic AF and less commonly used in asymptomatic patients, indicating consistency in clinical practice and AF guidelines. Moreover, concomitant anti-platelet drug use is common in asymptomatic patients, possibly because of the more prevalent distribution of CAD, PAD, and prior MI in the asymptomatic AF population. In our study, asymptomatic AF was predicted by male sex, long-standing persistent/permanent AF, medical history of stroke/TIA, PAD, prior bleeding, MI, and concomitant anti-platelet drug use, which may have practical implications from the perspective of screening strategies based on the appropriate targeting of the general population.[24]

Atrial fibrillation significantly increases the risk of stroke, and treating patients with AF with oral anti-coagulants effectively reduces stroke risk by approximately two-thirds.[4,6–10] Global guidelines recommend anti-coagulation when the stroke risk score calculated by the CHA_2DS_2-VASc score is above 1 in women and 2 in men.[25–28] In our study, asymptomatic AF was more common in patients with a previous stroke history; however, previous studies have confirmed a relatively low percentage of OAC therapy in this population.[29] Therefore, in clinical practice, patients with a history of previous stroke, especially those with asymptomatic AF, should be closely monitored for OAC therapy. More recent guidelines have moved towards a more holistic or integrated care approach to AF management, including appropriate anti-coagulation, rate or rhythm control, and comorbidity management, with improved clinical outcomes, including stroke reduction.[30–32]

Permanent AF is approximately three-fold more common in asymptomatic patients with AF, and persistent AF is approximately two-fold more common in symptomatic patients.[6] In this study, newly diagnosed AF and permanent AF were common among asymptomatic patients

Table 3 In-hospital outcomes associated with asymptomatic AF among patients

In-hospital events	Asymptomatic ($n = 4505$)	Symptomatic ($n = 48025$)	Overall ($n = 52530$)	*P*-value	Adjusted analysis		Sensitive-adjusted analysis[a]	
					aOR (95% CI)	*P*-value	aOR (95% CI)	*P*-value
All-cause death, *n* (%)	33 (0.7)	204 (0.4)	237 (0.5)	0.004	1.47 (1.00–2.14)	0.047	1.52 (1.05–2.20)	0.027
Ischaemic stroke or TIA, *n* (%)	53 (1.2)	347 (0.7)	400 (0.8)	0.001	1.43 (1.06–1.91)	0.018	1.44 (1.07–1.93)	0.016
ACS, *n* (%)	31 (0.7)	172 (0.4)	203 (0.4)	0.001	1.51 (1.02–2.22)	0.038	1.70 (1.15–2.51)	<0.001
Heart failure, *n* (%)	294 (6.5)	4142 (8.6)	4436 (8.5)	<0.001	0.71 (0.62–0.81)	<0.001	0.65 (0.57–0.73)	<0.001

The covariates included in the multivariable regression analysis were asymptomatic AF/symptomatic AF, age, sex, race, hospital levels, AF phenotypes, medical insurance, medical history of smoking, drinking, hypertension, diabetes mellitus, stroke/TIA, PAD, heart failure, CAD, previous major bleeding, prior MI, COPD, chronic renal disease, and prior treatment, including catheter ablation, surgical ablation, AADs use, electric cardioversion, and concomitant anti-platelet drug use before admission.
AADs, anti-arrhythmic drugs; ACS, acute coronary syndrome; AF, atrial fibrillation; aOR, adjusted odds ratio; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; PAD, peripheral artery disease; TIA, transient ischaemic attack.
[a]The covariates included in the sensitive multivariable regression analysis were asymptomatic AF/symptomatic AF, age, sex, in-hospital anti-coagulants, CHA_2DS_2-VASc score, admitted departments, HAS-BLED risk score, and AF phenotypes.

with AF, whereas paroxysmal AF was common in symptomatic patients, suggesting a different distribution of AF patterns among hospitalized Chinese patients with AF. In addition, asymptomatic patients with newly diagnosed AF may not be truly asymptomatic because of their unawareness or lack of health education and knowledge about AF. Asymptomatic patients may become anxious and depressed when they are diagnosed with AF and thus become symptomatic.[33,34] This also suggests the importance of health education about AF in the population.

The first presentation of individuals with AF can be accompanied by an acute stroke[35–37] or cardiomyopathy.[38] In this study, we focused on the main diagnosis among patients with AF seeking medical treatment. We discovered that the majority of asymptomatic patients were admitted with non-AF diagnoses, suggesting the importance of non-AF management among these patients. However, whether more intensive monitoring and comprehensive AF management, including increased quality of oral anti-coagulation and other medical interventions, can alter the in-hospital outcomes of these patients requires further investigation, although the current approach in the guidelines is to manage AF in a more holistic or integrated care manner.[27,39]

The relationship between asymptomatic AF and its prognosis remains controversial. Previously, asymptomatic AF was considered benign; thus, for a long time, AF guidelines focused on controlling symptomatic episodes as the main treatment goal. Nevertheless, recent studies have reported that asymptomatic AF increases all-cause mortality and stroke risk.[4,6–8] In a study by Boriani *et al.*,[6] asymptomatic patients were associated with a two-fold higher 1-year mortality compared with symptomatic patients. A meta-analysis that included >80 000 patients with AF reported no differences between symptomatic and asymptomatic patients regarding the risks of all-cause death and stroke.[40] More recently, study from Asia Pacific Heart Rhythm Society-AF registry that patients with AF as a primary symptom had lower mortality and/or stroke/TIA/peripheral embolism and mortality rates over a 1-year follow-up.[41] Our present study revealed that in-hospital clinical events, including all-cause mortality, ischaemic stroke/TIA, and ACS, were higher among patients with asymptomatic AF, and asymptomatic AF was related to these in-hospital clinical events. Hence, management strategies for patients with AF should not be based on their symptomatic clinical status alone.

Patients with AF and heart failure are a special category with highly prevalent clinical conditions that frequently coexist in a bidirectional manner.[42–44] To our knowledge, however, the relationship between asymptomatic AF and heart failure has not been reported. In this study, patients with a history of heart failure or LVEF ≤40% were commonly patients with symptomatic AF. In addition, symptomatic AF was closely related to in-hospital heart failure events. This may be because these patients had poorer cardiac function, lacked physical activity, and were more likely to perceive AF.

Limitations

This study had some limitations. First, the results of this study were derived from an observational study that described associations rather than causation. Second, our study was based on hospitalized Chinese patients with AF; therefore, the results cannot be easily extrapolated to other ethnicities, countries, or general population-based registries. Third, the diagnosis of AF type, determination of symptomatic/asymptomatic status, and classification of symptoms were physician-dependent at enrolment, which may have affected the clinical situation and outcomes. Fourth, despite conducting multivariable analysis, we could not exclude the possibility of unmeasured or residual confounders. Despite these limitations, our study provides the first population characteristics of asymptomatic AF in a Chinese hospitalized population and has some clinical implications.

Conclusions

Asymptomatic AF is common among hospitalized patients with AF. Asymptomatic clinical status is associated with male sex, comorbidities, and a higher risk of in-hospital outcomes. The adoption of management strategies for patients with AF should not be solely based on the presence or absence of symptomatic AF clinical status.

Supplementary material

Supplementary material is available at *Europace* online.

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Data availability

Raw data are available upon reasonable request with the corresponding author.

References

1. Alonso A, Bengtson LG. A rising tide: the global epidemic of atrial fibrillation. *Circulation* 2014;**129**:829–30.
2. Wynn GJ, Todd DM, Webber M, Bonnett L, McShane J, Kirchhof P *et al.* The European Heart Rhythm Association symptom classification for atrial fibrillation: validation and improvement through a simple modification. *Europace* 2014;**16**:965–72.
3. Ganapathy AV, Monjazeb S, Ganapathy KS, Shanoon F, Razavi M. "Asymptomatic" persistent or permanent atrial fibrillation: a misnomer in selected patients. *Int J Cardiol* 2015;**185**:112–3.
4. Esato M, Chun YH, An Y, Ogawa H, Wada H, Hasegawa K *et al.* Clinical impact of asymptomatic presentation status in patients with paroxysmal and sustained atrial fibrillation: the Fushimi AF registry. *Chest* 2017;**152**:1266–75.
5. Wallenhorst C, Martinez C, Freedman B. Risk of ischemic stroke in asymptomatic atrial fibrillation incidentally detected in primary care compared with other clinical presentations. *Thromb Haemost* 2022;**122**:277–85.
6. Boriani G, Laroche C, Diemberger I, Fantecchi E, Popescu MI, Rasmussen LH *et al.* Asymptomatic atrial fibrillation: clinical correlates, management, and outcomes in the EORP-AF Pilot General Registry. *Am J Med* 2015;**128**:509–18.e2.
7. Chen-Scarabelli C, Scarabelli TM, Ellenbogen KA, Halperin JL. Device-detected atrial fibrillation: what to do with asymptomatic patients? *J Am Coll Cardiol* 2015;**65**:281–94.
8. Noseworthy PA, Kaufman ES, Chen LY, Chung MK, Elkind MSV, Joglar JA *et al.* Subclinical and device-detected atrial fibrillation: pondering the knowledge gap: a scientific statement from the American Heart Association. *Circulation* 2019;**140**:e944–63.
9. Ben Freedman S, Lowres N. Asymptomatic atrial fibrillation: the case for screening to prevent stroke. *JAMA* 2015;**314**:1911–2.
10. Gladstone DJ, Spring M, Dorian P, Panzov V, Thorpe KE, Hall J *et al.* Atrial fibrillation in patients with cryptogenic stroke. *N Engl J Med* 2014;**370**:2467–77.
11. Hao Y, Liu J, Smith SC, Huo Y, Fonarow GC, Ge J *et al.* Rationale and design of the Improving Care for Cardiovascular Disease in China (CCC) project: a national registry to improve management of atrial fibrillation. *BMJ Open* 2018;**8**:e020968.
12. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC Jr *et al.* 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2019;**74**:104–32.
13. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF III, Feldman HI *et al.* A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;**150**:604–12.
14. Kitsiou A, Rogalewski A, Kalyani M, Deelawar S, Tribunyan S, Greeve I *et al.* Atrial fibrillation in patients with embolic stroke of undetermined source during 3 years of prolonged monitoring with an implantable loop recorder. *Thromb Haemost* 2021;**121**:826–33.
15. Kalarus Z, Mairesse GH, Sokal A, Boriani G, Średniawa B, Casado-Arroyo R *et al.* Searching for atrial fibrillation: looking harder, looking longer, and in increasingly sophisticated ways. An EHRA position paper. *Europace* 2023;**25**:185–98.
16. Kiliszek M, Uziębło-Życzkowska B, Gorczyca I, Maciorowska M, Jelonek O, Wożakowska-Kapłon B *et al.* Symptomatic and asymptomatic patients in the Polish Atrial Fibrillation (POL-AF) registry. *J Clin Med* 2021;**10**:1091.
17. Gibbs H, Freedman B, Rosenqvist M, Virdone S, Mahmeed WA, Ambrosio G *et al.* Clinical outcomes in asymptomatic and symptomatic atrial fibrillation presentations in GARFIELD-AF: implications for AF screening. *Am J Med* 2021;**134**:893–901.e11.
18. Ko D, Rahman F, Schnabel RB, Yin X, Benjamin EJ, Christophersen IE. Atrial fibrillation in women: epidemiology, pathophysiology, presentation, and prognosis. *Nat Rev Cardiol* 2016;**13**:321–32.
19. Ballatore A, Matta M, Saglietto A, Desalvo P, Bocchino PP, Gaita F *et al.* Subclinical and asymptomatic atrial fibrillation: current evidence and unsolved questions in clinical practice. *Medicina (Kaunas)* 2019;**55**:497.
20. Flaker GC, Belew K, Beckman K, Vidaillet H, Kron J, Safford R *et al.* Asymptomatic atrial fibrillation: demographic features and prognostic information from the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study. *Am Heart J* 2005;**149**:657–63.
21. Potpara TS, Polovina MM, Marinkovic JM, Lip GY. A comparison of clinical characteristics and long-term prognosis in asymptomatic and symptomatic patients with first-diagnosed atrial fibrillation: the Belgrade Atrial Fibrillation Study. *Int J Cardiol* 2013;**168**:4744–9.
22. Roberts JD, Vittinghoff E, Lu AT, Alonso A, Wang B, Sitlani CM *et al.* Epigenetic age and the risk of incident atrial fibrillation. *Circulation* 2021;**144**:1899–911.
23. Ward-Caviness CK. Accelerated epigenetic aging and incident atrial fibrillation: new outlook on an immutable risk factor? *Circulation* 2021;**144**:1912–4.
24. Schnabel RB, Marinelli EA, Arbelo E, Boriani G, Boveda S, Buckley CM *et al.* Early diagnosis and better rhythm management to improve outcomes in patients with atrial fibrillation: the 8th AFNET/EHRA consensus conference. *Europace* 2023;**25**:6–27.
25. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C *et al.* ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the task force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J* 2021;**42**:373–498.
26. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC Jr *et al.* 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons. *Circulation* 2019;**140**:e125–51.
27. Chao TF, Joung B, Takahashi Y, Lim TW, Choi EK, Chan YH *et al.* 2021 Focused update consensus guidelines of the Asia Pacific Heart Rhythm Society on stroke prevention in atrial fibrillation: executive summary. *Thromb Haemost* 2022;**122**:20–47.
28. Steffel J, Collins R, Antz M, Cornu P, Desteghe L, Haeusler KG *et al.* 2021 European Heart Rhythm Association practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Europace* 2021;**23**:1612–76.
29. Guo Y, Kotalczyk A, Imberti JF, Wang Y, Lip GY. Quality indicators in the management of elderly Chinese patients with atrial fibrillation: a report from the Optimal Thromboprophylaxis in Elderly Chinese Patients with Atrial Fibrillation (ChiOTEAF) registry. *Eur Heart J Qual Care Clin Outcomes* 2022;**8**:651–8.
30. Romiti GF, Pastori D, Rivera-Caravaca JM, Ding WY, Gue YX, Menichelli D *et al.* Adherence to the 'atrial fibrillation better care' pathway in patients with atrial fibrillation: impact on clinical outcomes—a systematic review and meta-analysis of 285,000 patients. *Thromb Haemost* 2022;**122**:406–14.
31. Guo Y, Imberti JF, Kotalczyk A, Wang Y, Lip GY. Atrial fibrillation better care pathway adherent care improves outcomes in Chinese patients with atrial fibrillation. *JACC: Asia* 2022;**2**:422–9.
32. Patel SM, Palazzolo MG, Murphy SA, Antman EM, Braunwald E, Lanz HJ *et al.* Evaluating the atrial fibrillation better care pathway in the ENGAGE AF-TIMI 48 trial. *Europace* 2022;**24**:1730–8.
33. Lane DA, Langman CM, Lip GY, Nouwen A. Illness perceptions, affective response, and health-related quality of life in patients with atrial fibrillation. *J Psychosom Res* 2009;**66**:203–10.
34. Thrall G, Lip GY, Carroll D, Lane D. Depression, anxiety, and quality of life in patients with atrial fibrillation. *Chest* 2007;**132**:1259–64.
35. Sanna T, Diener HC, Passman RS, Di Lazzaro V, Bernstein RA, Morillo CA *et al.* Cryptogenic stroke and underlying atrial fibrillation. *N Engl J Med* 2014;**370**:2478–86.
36. Scheuermeyer FX, Mackay M, Christenson J, Grafstein E, Pourvali R, Heslop C *et al.* There are sex differences in the demographics and risk profiles of emergency department (ED) patients with atrial fibrillation and flutter, but no apparent differences in ED management or outcomes. *Acad Emerg Med* 2015;**22**:1067–75.
37. AlTurki A, Marafi M, Russo V, Proietti R, Essebag V. Subclinical atrial fibrillation and risk of stroke: past, present and future. *Medicina (Kaunas)* 2019;**55**:611.
38. Xiong Q, Proietti M, Senoo K, Lip GY. Asymptomatic versus symptomatic atrial fibrillation: a systematic review of age/gender differences and cardiovascular outcomes. *Int J Cardiol* 2015;**191**:172–7.
39. Chao TF, Nedeljkovic MA, Lip GYH, Potpara TS. Stroke prevention in atrial fibrillation: comparison of recent international guidelines. *Eur Heart J Suppl* 2020;**22**:O53–O60.
40. Sgreccia D, Manicardi M, Malavasi VL, Vitolo M, Valenti AC, Proietti M *et al.* Comparing outcomes in asymptomatic and symptomatic atrial fibrillation: a systematic review and meta-analysis of 81,462 patients. *J Clin Med* 2021;**10**:3979.
41. Tse HF, Teo WS, Siu CW, Lip GY. Prognosis and treatment of atrial fibrillation in Asian cities: 1-year review of the Asia-Pacific Heart Rhythm Society Atrial Fibrillation Registry. *Europace* 2022;**24**:1889–98.
42. Santhanakrishnan R, Wang N, Larson MG, Magnani JW, McManus DD, Lubitz SA *et al.* Atrial fibrillation begets heart failure and vice versa: temporal associations and differences in preserved versus reduced ejection fraction. *Circulation* 2016;**133**:484–92.
43. Carlisle MA, Fudim M, DeVore AD, Piccini JP. Heart failure and atrial fibrillation, like fire and fury. *JACC Heart Fail* 2019;**7**:447–56.
44. Benjamin EJ, Chen PS, Bild DE, Mascette AM, Albert CM, Alonso A *et al.* Prevention of atrial fibrillation: report from a national heart, lung, and blood institute workshop. *Circulation* 2009;**119**:606–18.