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Yang, Wang-Yang; Du, Xin; Fawzy, Ameenathul M; He, Liu; Li, Hong-Wei; Dong, Jian-Zeng; Lip, Gregory Y H; Ma, Chang-Sheng; Chinese Atrial Fibrillation Registry Study Group

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Jian zeng Dong ORCID iD: 0000-0001-7299-7805

Gregory Lip ORCID iD: 0000-0002-7566-1626

Chang Sheng Ma ORCID iD: 0000-0001-6966-6239

Associations of Atrial Fibrillation Progression with Clinical Risk Factors and Clinical Prognosis: A report from the Chinese Atrial Fibrillation Registry Study

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Wang-Yang Yang, MD[1,2,3]; Xin Du, MD[2†]; Ameenathul M Fawzy, MB[3]; Liu He, PhD[2]; Hong-Wei Li, MD[1]; Jian-Zeng Dong, MD[2]; Gregory Y.H. Lip, MD[4,5*†]; Chang-Sheng Ma, MD[2*†]; The Chinese Atrial Fibrillation Registry Study Group.

[*Co-corresponding authors; † joint senior authors.]

[1]Department of Cardiology, Cardiovascular Center, Beijing Friendship Hospital, Capital Medical University, Beijing, China; [2]Department of Cardiology, Beijing AnZhen Hospital, Capital Medical University, National Clinical Research Centre for Cardiovascular Diseases, Beijing, China; [3]Institute of Applied Health Research,

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University of Birmingham, United Kingdom; [4]Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, United Kingdom; [5]Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

Address for Correspondence:

Professor Chang-Sheng Ma

Department of Cardiology, Beijing AnZhen Hospital, Capital Medical University

No.2 Beijing Anzhen Road, Chaoyang District, Beijing, P.R. China, 100029

Tel (office): 86-10-84005363

Fax (office & secretariat): 86-10-84005361

E-mail: chshma@vip.sina.com

Professor Gregory Y.H. Lip

Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, L14 3PE, United Kingdom

E-mail: gregory.lip@liverpool.ac.uk

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Declaration of Competing Interest

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Data Availability Statement

The research data are not shared due to ethical restrictions.

Abstract

Background: An understanding of the risk factors for atrial fibrillation (AF) progression and the associated impacts on clinical prognosis are important for the future management of this common arrhythmia. We aimed to investigate the rate of progression from paroxysmal (PAF) to more sustained sub-types of AF (SAF), the associated risk factors for this progression, and its impact on adverse clinical outcomes.

Methods and Results: Using data from the Chinese Atrial Fibrillation Registry study, we included 8290 PAF patients. Half of them underwent initial AF ablation at enrollment. Main outcomes were ischemic stroke/systemic embolism (IS/SE), cardiovascular hospitalization, cardiovascular death, and all-cause mortality. The median follow-up duration was 1091 (704, 1634) days, and progression from PAF to SAF occurred in 881 (22.5%) non-ablated patients, while 130 (3.0%) ablated patients had AF recurrence and developed SAF. The incidence rate of AF progression for the cohort was 3.87 (95%CI: 3.64-4.12) per 100 patient-years, being higher in non-ablated compared to ablated patients. Older age, longer AF history, heart failure, hypertension, coronary artery disease, respiratory diseases, and larger atrial diameter were associated with higher incidence of AF progression, while antiarrhythmic drug use and AF ablation were inversely related to it. For non-ablated patients, AF progression was independently associated with an increased risk of IS/SE (HR 1.52, 95%CI: 1.15-2.01) and cardiovascular hospitalizations (HR 1.40, 95%CI:1.23-1.58).

Conclusions: AF progression was common in its natural course. It was related to comorbidities and whether rhythm control strategies were used, and was associated with an increased risk of IS/SE and cardiovascular hospitalization.

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Key Words: Atrial fibrillation; progression; prognosis; ablation; risk factor.

Background

Atrial fibrillation (AF) is the most common cardiac arrhythmia in clinical practice, leading to a major healthcare burden from stroke, heart failure, hospitalizations, and mortality[1]. Based on the characteristics of its episodes that range from short, infrequent attacks to longer, more frequent ones, AF can be classified into four sub-types: paroxysmal, persistent, long-standing persistent, and permanent AF[2]. In terms of the natural course, progression from paroxysmal to more sustained sub-types of AF can be observed in many patients while in a small proportion of patients, AF seems to remain paroxysmal over several decades[3]. And the course can be very different for patients under rhythm control treatment, especially AF ablation[4].

The focus on AF progression is of importance as this can have potential implications on adverse clinical outcomes[5, 6]. There are limited data reporting the incidence of AF progression and its influences on clinical outcomes. Owing to the

heterogeneity of studies, reported risk factors associated with AF progression have varied. The role of rhythm control treatment, including antiarrhythmic drug use and catheter ablation, in the prevention of AF progression and its associated AF-related complications is unclear. An understanding of the risk factors for arrhythmia progression in patients with AF and the associated impacts on clinical prognosis is important for the future management of this common arrhythmia.

The Chinese Atrial Fibrillation Registry (China-AF) study [7] is one of the largest prospective registry studies consisting of patients with AF, providing an opportunity to follow the real-world condition of these patients. Using data from the China-AF study, we aimed to investigate the rate of progression from paroxysmal (PAF) to more sustained sub-types of AF (SAF), the associated risk factors for this progression, and its impact on adverse clinical outcomes.

Methods

Study Population

The design of the China-AF study has been described previously[7]. In brief, this was a prospective registry study involving 31 tertiary and non-tertiary hospitals in Beijing, China. All patients with confirmed diagnosis of AF were enrolled from both outpatient and inpatient settings in the participating hospitals. AF ablation was provided in 18/31 (58%) of participating hospitals. Whether to undergo AF ablation

was at the discretion of both patients and their treating cardiologists. In general, the procedure was recommended to relieve AF related symptoms. The China-AF study was reviewed and approved by the Ethics Committee of Beijing Anzhen Hospital. Written consents were obtained from all patients. Only anonymized data were used in our analysis.

Consecutive adult patients with PAF enrolled in the China-AF study between August 2011 and December 2017 were deemed eligible. Patients with AF ablation history, or no clear determination whether or not have AF ablation at enrolment, or no baseline echocardiography examinations, or follow-up time of less than one year were excluded. Thus, patients who had not undergone AF ablation from their enrolment to the end of followup (non-ablated patients) and patients who underwent initial AF ablation immediately after enrolment (ablated patients) were all included in our study. Flow chart of inclusions, exclusions, and follow-up processes are summarised in **Figure-1**.

All baseline characteristics were recorded upon enrolment. The CHA_2DS_2-VASc score (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior thromboembolism, vascular disease, female sex, and age 65-74 years) was used to stratify the risk of thromboembolism.[8]

Follow-up data collection

The index date was defined as the date of enrolment in the study and follow-up visits were routinely scheduled every 6 months thereafter. Clinical information including ECG data, symptoms associated with the duration and frequency of AF episodes, and adverse clinical outcomes were collected by trained cardiovascular physicians and nurse practitioners at outpatient clinics or through telephone interviews every 6 months. In the China-AF study, ECG and/ or 24h-Holter monitors were undertaken as part of periodic clinical checks at least once every 6 months, no matter there were symptoms or not. Symptom-triggered ECGs performed whenever patients felt symptoms of AF, and opportunistic ECGs which were recorded for other purposes such as physical examination were also collected.

Definitions

In our study, PAF or SAF was diagnosed by the practitioners at each visit, on the basis of both ECG results and symptoms. In general, PAF was defined as AF episodes with subsequent demonstration of reversion to sinus rhythm within 7 days. For the purpose of analysis, sub-types including persistent AF, long-standing persistent AF, and permanent AF were classed as 'more sustained AF (SAF)' instead of being distinguished individually. Patients were classed as having SAF if they had evidence of AF episodes lasting for more than 7 days on recorded ECG. For those patients who do not have long-time ECG records and can not accurately define the onset and end of

AF episodes by symptoms, were recognized as SAF if they were still in AF at the next half-year visit without an ECG record of sinus rhythm in the interim.

AF progression was defined as a change from PAF to SAF during follow-up. For patients with AF progression, the follow-up phase was divided into three parts: the pre-progression period, defined as the period between enrolment and time of the last diagnosis of PAF; the peri-progression period, defined as the 6-months period over which the transition from PAF to SAF occurred; and the post-progression period, defined as the period which was the course following the first diagnosis of SAF.

Adverse clinical outcomes comprised of ischemic stroke/ systemic embolism (IS/SE), cardiovascular hospitalization, cardiovascular death, and all-cause mortality. Events were adjudicated by an independent committee. The detailed definitions of those events were provided in **Supplementary material online**.

Statistical Analysis

Baseline characteristics were presented as mean ± SD or median (quartile1, quartile3) for continuous variables, numbers (percentages) for categorical variables, and T-tests, Wilcoxon rank sum tests, and Chi-squared (χ^2) tests were used accordingly. Cumulative incidence of AF progression was presented with a Kaplan-Meier curve. The incidence of AF progression was calculated by dividing numbers of patients with AF progression by person-years at risk, and the incidence of the clinical outcome was

calculated by dividing numbers of events by person-years at risk, with the 95% confidence interval (CI) estimated using a Poisson model.

Univariable and multivariable Cox regressions were used to identify risk factors independently associated with AF progression. Covariates included in the multivariable model 1 were broadly categorized into baseline sociodemographic characteristics and comorbidities that were significantly associated with AF progression in our univariable analysis and previously published studies. Hence, the covariates chosen for this model were age, female sex, interval since the first detection of AF, congestive heart failure, hypertension, diabetes mellitus, coronary artery disease, valvular heart disease, and respiratory diseases. In multivariable model 2, in addition to the covariates used in model 1, data on echocardiography parameters (Left atrial diameter ≥45 mm, and left ventricular ejection fraction ≤40%), medications at baseline (antiarrhythmic drugs, including Sotalol or Propafenone or Amiodarone), non-pharmacotherapy at enrolment (AF ablation), and lifestyle history (drinking, smoking), that might have contributions to the AF progression were included.

We also performed a further multivariate analysis using the Cox proportional hazards model to evaluate the association between AF progression and adverse clinical outcomes, and the covariates chosen to be adjusted for this were age, female sex, history of thromboembolism, congestive heart failure, hypertension, diabetes

mellitus, coronary artery disease, peripheral artery disease and prescription of oral anticoagulants such as the non-vitamin K antagonist oral anticoagulants (NOACs) or warfarin at baseline. All analyses were performed using SAS software version 9.4 (SAS Institute, Cary, North Carolina) and a P-value of <0.05 was considered statistically significant.

Results

The China-AF study enrolled 13691 consecutive patients with PAF between August 2011 and December 2017. After exclusion of 1055 patients with AF ablation history, 913 patients without clear determination whether or not have AF ablation at enrolment or during follow-up, 2071 patients without baseline echocardiography examinations, and 1362 patients with follow-up time of less than one year, we finally included 8290 patients in our analysis. Of these, 4379 patients underwent initial AF ablation at enrolment, while 3911 patients had no AF ablation. During a median follow-up time of 1091 (704, 1634) days, progression from PAF to SAF occurred in 1011 (12.2%) patients in total, comprising 881 (22.5%) non-ablated patients and 130 (3.0%) ablated patients who had AF recurrence after a single ablation procedure and developed SAF (**Figure-1**).

The incidence of AF progression for the cohort was 3.87 (95%CI: 3.64-4.12) per 100 patient-years; for non-ablated patients, it was 7.15 (95%CI: 6.69-7.63) per 100

patient-years. On Kaplan-Meier analysis, the cumulative rates of AF progression at 1, 2, and 3 years for all patients were 5.89%, 8.84%, and 11.38%, respectively; and for non-ablated patients, the progression rates were 10.80%, 16.06%, and 20.38%, respectively (**Figure-2**).

Patients with AF progression were older, more likely to be female, had longer interval since first detection of AF, bigger body mass index (BMI), more clinical comorbidities and larger left atrial diameter (LAD); but fewer alcohol drinkers, smokers, lower left ventricular ejection fraction (LVEF), lower proportion of prescriptions of propafenone, amiodarone, NOACs, and less AF ablation, compared with patients without AF progression **(Table-1).** A significant difference was observed in the distribution of CHA_2DS_2-VASc score between the two groups ($P<0.001$). Baseline characteristics stratified by AF ablation can be found in **Supplementary material online eTable-1**.

Risk factors associated with AF progression

For all our patients, the univariable analysis showed that age ≥ 75 years, female sex, interval since the first detection of AF ≥ 1 years, congestive heart failure, hypertension, diabetes mellitus, coronary artery disease, valvular heart disease, respiratory disease, drinking, smoking, LAD ≥ 45mm, LVEF ≤ 40%, antiarrhythmic

drugs, and AF ablation were associated or had an inverse association with AF progression (**Table-2**).

On multivariate model 1, age ≥ 75 years, interval since the first detection of AF ≥ 1 years, congestive heart failure, hypertension, coronary artery disease, and respiratory disease were significantly associated with increased risk of AF progression. On multivariate model 2, age ≥ 75 years (HR1.48, 95%CI: 1.29, 1.71), interval since the first detection of AF≥ 1 years (HR1.34, 95%CI: 1.17, 1.53), congestive heart failure (HR1.86, 95%CI: 1.57, 2.21), hypertension (HR1.24, 95%CI: 1.07, 1.45), respiratory disease (HR1.34, 95%CI: 1.11, 1.61), and LAD ≥ 45 mm (HR1.81, 95%CI: 1.56, 2.10) were all associated with higher incidence of AF progression. In contrast, AF ablation (HR0.18, 95%CI: 0.15, 0.22) was associated with lower incidence of AF progression.

For non-ablated patients, similar results were found in univariable and multivariable analysis (**Supplementary material online eTable-2**); On multivariate model 2, age ≥ 75 years (HR1.45, 95%CI: 1.25, 1.69), interval since the first detection of AF≥1 years (HR1.31, 95%CI: 1.13, 1.51), congestive heart failure (HR1.84, 95%CI: 1.54, 2.19), hypertension (HR1.27, 95%CI: 1.07, 1.50), coronary artery disease (HR1.25, 95%CI: 1.01, 1.55), respiratory disease (HR1.36, 95%CI： 1.12, 1.65), and LAD ≥ 45 mm (HR1.78, 95%CI: 1.52, 2.09) were found to be associated with higher incidence of AF

progression. Antiarrhythmic drugs (HR0.79, 95%CI: 0.67, 0.95) were associated with a lower incidence of AF progression.

Adverse clinical outcomes

The incidence of the adverse clinical outcomes in non-ablated patients, stratified by the phases of AF progression, are summarised in **Figure-3**. More than half of the patients who underwent AF ablation were monitored with no AF recurrence in our study. Given the prognosis of patients with and without AF would be different, we only analyzed the adverse clinical outcomes of non-ablated patients to evaluate the association of AF progression with clinical prognosis.

For AF progression group, IS/SE events occurred in 94 patients: 22 during the pre-progression period, 23 during the peri-progression period and 49 during the post-progression period; thus, incidence rates were 1.48 (95%CI: 0.97-2.24), 5.22 (95%CI: 3.47-7.86), and 1.88 (95%CI: 1.42-2.49) per 100 person-years, respectively. For patients without AF progression, 134 IS/SE events were recorded, and the corresponding incidence rate was 1.20 (95CI: 1.01-1.42) per 100 person-years.

Cardiovascular hospitalization occurred in 533 patients in the AF progression group; 111 during the pre-progression period, 149 in the peri-progression period, and 273 during the post-progression period. The incidence rates were 8.05 (95%CI: 6.68-9.69), 33.83 (95%CI: 28.81-39.72), and 12.46 (95%CI: 11.06-14.03) per 100

person-years, respectively. For the patients without AF progression, 799 patients had cardiovascular hospitalization with an incidence rate of 8.21 (95%CI: 7.66-8.80) per 100 person-years.

Five and 96 cardiovascular deaths occurred in the peri- and post-progression periods respectively. The corresponding incidence rates were 1.36 (95%CI: 0.61-3.03) and 5.94 (95%CI: 5.07-6.95) per 100 person-years, respectively. In the PAF without progression group, cardiovascular death occurred in 134 patients, at an incidence rate of 2.42 (95%CI: 2.15-2.72) per 100 person-years.

The numbers for all-cause mortality in the PAF with progression group, in peri- and post-progression periods were 6 and 154, with corresponding incidence rates of 1.14 (95%CI: 0.47-2.73) and 3.65 (95%CI: 2.99-4.46) per 100 person-years, respectively. In total, 274 all-cause mortality events occurred in the PAF without progression group and the incidence rate was 1.18 (95%CI: 0.99-1.39) per 100 person-years.

On multivariate Cox regression analysis (**Table-3**), AF progression was significantly associated with an increased risk of IS/SE (HR1.52, 95%CI: 1.15, 2.01) and cardiovascular hospitalization (HR1.40, 95%CI:1.23, 1.58), even after multivariable adjustments.

Discussion

As far as we are aware, the present study is the largest prospective cohort evaluating the clinical correlates of AF progression, including a comparable number of patients in their natural course and patients who underwent single AF ablation. The principal findings were as follows: (i) The incidence of AF progression for the cohort was 3.87 (95%CI: 3.64-4.12) per 100 patient-years, being higher in non-ablated compared to ablated patients; (ii) AF progression was associated with an increased risk of IS/SE and cardiovascular hospitalization; (iii) Age at diagnosis ≥ 75 years, interval since the first detection of AF ≥ 1 years, congestive heart failure, hypertension, coronary artery disease, respiratory diseases, and LAD ≥ 45 mm were associated with a higher incidence of AF progression, while antiarrhythmic drug use and AF ablation were inversely related to AF progression.

AF episodes often increase in frequency and duration, resulting in a proportion of patients developing a more sustained type of AF over time[2]. An understanding of the progression course of AF and its clinical impact is important for the future management of this disease. However, the prevalence of AF progression varies from population to population. In the EuroHeart survey, de Vos et al[5] reported that progression of AF occurred in 178 (15%) patients at 1-year follow-up, and developed the HATCH score from this population. However, such a short term evaluation can not give out a comprehensive picture of the process of AF progression. In a recent meta-analysis[9] including 47 studies with 27266 patients who were followed up for

105912 patient-years, the incidence of AF progression was reported to be 7.1 per 100 patient-years. In the Fushimi AF registry, Ogawa et al[10] reported that AF progression occurred in 252 (12.77%) patients during a median follow-up period of 1105 days (4.22 per 100 person-years). Using data from two cohort studies in Switzerland, Steffen et al[4] found that the incidence of AF progression was 4.9 per 100 person-years during a median follow-up of 3.0 years. In that study, however, 26% of their patients had prior pulmonary vein isolation (PVI) and 15.8% underwent PVI during follow-up, but AF progression incidence was not reported separately. In contrast, we reported the incidence of AF progression separately for ablated and non-ablated patients who were under the same follow-up and evaluation protocol.

Risk factors associated with AF progression

Risk factors by affecting the natural course of AF could eventually alter the clinical decision making in these patients. Despite older age being regarded as one of the most common risk factors, the interval since the first detection of AF was found to be significantly associated with AF progression, superior to age[10]. Time-dependent pathophysiological mechanisms of AF development may be one of the possible explanations[11]. Left atrial enlargement has been identified as another common risk factor[10]. Patients with more sustained sub-types of AF have been found to have a greater tendency to increased fibrosis[12]. Larger LAD may be a sign of a more advanced stage of atrial fibrosis. Co-existing conditions such as congestive heart

failure, hypertension, coronary artery disease, and respiratory diseases were also risk factors in our cohort and could contribute to the electrical and structural remodeling process[13].

Obesity was not a risk factor of AF progression in our study but has been reported in previous studies[4, 6]. Similarly, there was no significant association between bigger body weight and AF progression in a Japanese cohort[10]. The possibility remains that the role of obesity in AF progression could be different in an Asian population.

Rhythm control treatments including antiarrhythmic drug use and AF ablation were shown to be associated with lower incidence of AF progression in our cohort, suggesting that these may be protective factors. Indeed, the Record-AF study[14] showed that AF rhythm at enrolment was an independent risk factor associated with the progression of AF. Also, the lack of rhythm control management (antiarrhythmic drugs or ablation) increased progression from paroxysmal or persistent AF to permanent AF[9, 15, 16]. Thus, performing AF ablation in the PAF phase may potentially slow the progression of AF to its permanent form by reducing AF burden and the following process of atrial fibrosis[17].

Clinical outcomes

In the present study, AF progression was significantly associated with an increased risk of IS/SE and cardiovascular hospitalization, with the incidence rates of these

events highest during the peri-progression period. Although patients with AF progression had higher CHA_2DS_2-VASc scores, AF progression was still independently associated with IS/SE events after adjustments were made for all comorbidities included in the score. These observations are similar to those observed by Ogawa et al[10], where the risk of IS/SE and hospitalization for heart failure were increased during the peri-progression period, subsequently declining in the post-progression period, to levels equivalent to patients with SAF at baseline. Based on data from the Belgrade AF Study, Potpara et al[18] reported that progression of AF, either paroxysmal becoming persistent or permanent, or persistent becoming permanent, was a predictor of thromboembolic events and the development of heart failure. PAF has been independently associated with a lower incidence of IS/SE events in Japanese population, compared to SAF[19].

As we can see from the baseline characteristics that patients with progression were much less likely to be on OAC. That may be explained by patients with AF progression were more 'complicated' clinically (eg.) with coronary artery disease, and may be already taking antiplatelet drugs, such as aspirin or clopidogrel. The high risk of bleeding while taking aspirin and OAC in combination may be one reason they were not prescribed OAC. However, since we did not collect information of medications during follow-up, we cannot analyze the impact of OAC on the risk of IS/SE.

The impact of AF sub-types on clinical events may be explained by arrhythmia burden which is likely to be much less in patients with PAF than those with SAF. Thromboembolism risk seems to be a quantitative function of AF burden, whereby longer and more frequent AF attacks increase the risk[20]. In the meantime, AF episodes correlate with rate-related cardiac dysfunction, thus precipitating and exacerbating each other through mechanisms such as electrical and structural remodeling[17]. Indeed, the progression of AF may be a reflection of this remodeling process, with higher rate of adverse clinical outcomes, suggesting the instability of electrical activity and cardiac function during this period.

Interventions to address modifiable risk factors and prevent or slow AF progression should be part of the holistic and integrated care approach for AF management. More aggressive control of comorbidities mentioned above and appropriate rhythm control strategies may slow the AF progression. However, we cannot overlook the side effects of long-term oral antiarrhythmic drug use. Although AF ablation was found to be associated with lower incidence of AF progression, left atrial appendage volume was found increased after AF ablation[17], which may cause worse hemodynamics. These things make the clinical benefit of rhythm control treatment uncertain. Further studies are needed to evaluate whether rhythm control strategies may improve the prognosis by slowing AF progression.

Limitations

Although the inclusion of a large number of patients undergoing AF ablation is an important strength of the present study when it comes to assessing AF progression in the presence of rhythm control, the potential selection bias introduced in this process should be acknowledged. Semi-annual assessment of AF type in a large number of patients with AF is another key strength of our study. However, patients with silent AF episodes lasting for more than 7 days may still be missed. Furthermore, we did not have records for the exact dates of the 'actual' AF progression, which may have been asymptomatic and could have occurred at any point during the 6-month peri-progression period. Drug treatments during follow-up were at the discretion of registered physicians and were not adjusted for clinical outcomes. Thus, we cannot determine whether antiarrhythmic drug use may improve the prognosis. Also, we had no data on the time in therapeutic range for individual patients taking warfarin.

Conclusion

In its natural course, AF progression from PAF to SAF is common, occurring in 1 in 5 patients over 3 years. Arrhythmia progression was related to comorbidities and whether rhythm control strategies were used, and was associated with an increased risk of IS/SE and cardiovascular hospitalization.

Group Members

Chao Jiang, MD; Shi-Jun Xia, MD; San-Shuai Chang, MD; Xin Zhao,MD; Xue-Yuan Guo, MD; Song-Nan Li, MD; Ri-Bo Tang, MD; Nian Liu, MD; Rong Bai, MD; Cai-Hua Sang, MD; Chen-Xi Jiang, MD; Rong-Hui Yu, MD; De-Yong Long, MD; and other members of the Chinese Atrial Fibrillation Registry Study Group.

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Figures

Figure-1. Flow chart of study patients.

Flow chart showing details of inclusions, exclusions, and follow-up process.

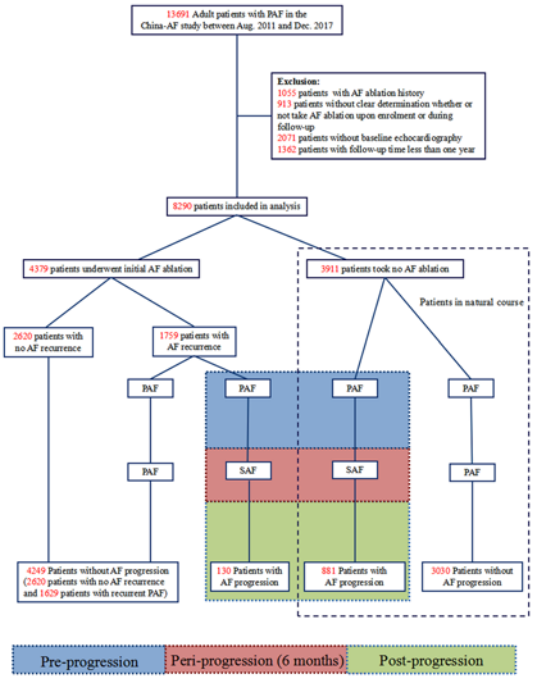

Figure-2. AF progression by Kaplan-Meier curve.

The plot of cumulative AF progression for (A) the entire cohort; (B) patients with AF ablation versus patients without ablation.

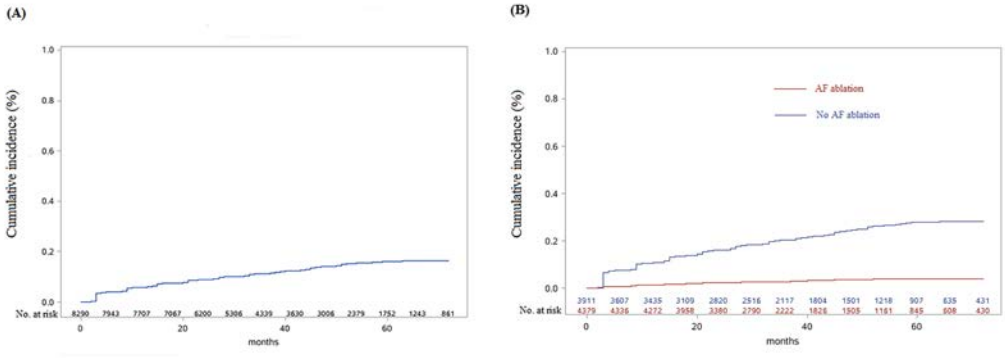

Figure-3. Incidence of adverse clinical outcomes in non-ablated PAF patients.

Histogram of incidence rate of adverse clinical outcomes in PAF patients without ablation, stratified by the phases of AF progression. (IS/SE, ischemic stroke/ systemic embolism)

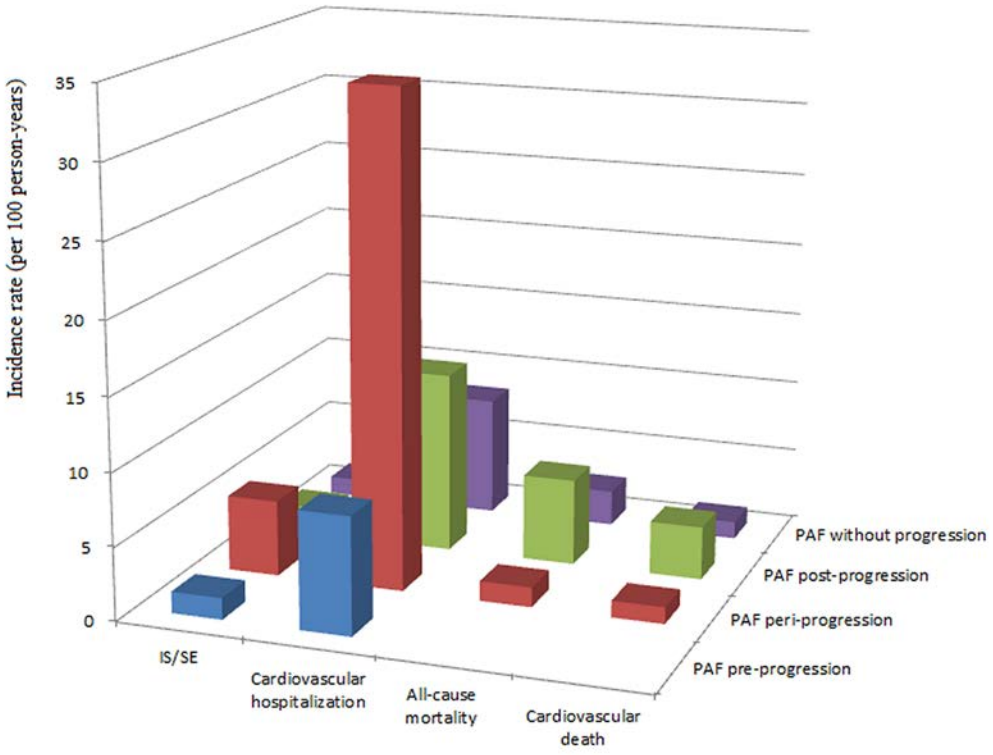

Table-1. Baseline characteristics of patients with or without AF progression.

	Patients with AF progression （n=1011）	**Patients without AF progression （n=7279）**	**P value**

Age, years, mean±SD	69.2 ± 11.0	62.7 ± 11.8	< 0.001
1-64, y, n (%)	303 (30.0)	3948 (54.2)	< 0.001
65-74, y, n (%)	321 (31.7)	2147 (29.5)	
≥ 75, y, n (%)	387 (38.3)	1184 (16.3)	
Female, n (%)	469 (46.4)	2941 (40.4)	< 0.001
Interval since first detection of AF, years, median (Q1, Q3)	2.5 (0.7, 6.6)	1.7 (0.3, 4.9)	< 0.001
BMI, kg/m², mean±SD	25.5 ± 3.9	25.3 ± 3.5	0.002
< 24, kg/m², n (%)	296 (33.3)	2444 (35.2)	0.409
24-28, kg/m², n (%)	406 (45.7)	3162 (45.5)	
≥ 28, kg/m², n (%)	186 (21.0)	1345 (19.3)	
Comorbidities, n (%)			

Congestive heart failure	252 (24.9)	499 (6.9)	< 0.001
Hypertension	762 (75.4)	4382 (60.2)	< 0.001
Diabetes mellitus	289 (28.6)	1609 (22.1)	< 0.001
Coronary artery disease	263 (26.0)	1068 (14.7)	< 0.001
Myocardial infarction	80 (7.9)	198 (2.7)	< 0.001
Peripheral artery disease	9 (0.9)	43 (0.6)	0.258
Prior thromboembolism	209 (20.7)	890 (12.2)	< 0.001
Valvular heart disease	159 (15.7)	577 (7.9)	< 0.001
PSVT	14 (1.4)	155 (2.1)	0.116
Respiratory diseases	141 (14.0)	530 (7.3)	< 0.001
Risk stratification			

CHA_2DS_2VASc score, median (Q1, Q3)	3.0 (2.0, 5.0)	2.0 (1.0, 3.0)	< 0.001
0, n (%)	47 (4.6)	1050 (14.4)	< 0.001
1, n (%)	116 (11.5)	1734 (23.8)	
≥ 2, n (%)	848 (83.9)	4495 (61.8)	
Lifestyle, n (%)			
Drinking	141 (14.0)	1241 (17.1)	0.013
Smoking	124 (12.3)	1073 (14.7)	0.036
Echocardiogram, mean ± SD			
Left atrial diameter, mm	41.5 ± 6.9	38.4 ± 5.7	< 0.001
Ejection fraction,%	62.0 ± 9.4	64.3 ± 7.4	< 0.001
Medication history, n (%)			

Antiarrhythmic drug			
Sotalol	19 (1.9)	142 (2.0)	0.877
Propafenone	90 (8.9)	1907 (26.2)	< 0.001
Amiodarone	147 (14.5)	1432 (19.7)	< 0.001
Anti-thrombotic drugs			
NOACs	33 (3.3)	1804 (24.8)	< 0.001
Warfarin	416 (41.2)	3215 (44.2)	0.070
Non-pharmacotherapy, n (%)			
AF ablation	130 (12.9)	4249(58.4)	< 0.001

PAF, paroxysmal atrial fibrillation; BMI, body mass index; PSVT, paroxysmal supraventricular tachycardia; ACEI/ARB, angiotensin converting enzyme inhibitors/angiotensin II receptor blockers; NOACs, non-vitamin K antagonist oral anticoagulants.

Table-2. Univariable vs. Multivariable Cox regression analysis of risk factors associated with AF progression for all patients.

	Univariate		**Multivariate**			
			Model 1		**Model 2**	
	HR (95%CI)	**P value**	**HR (95%CI)**	**P value**	**HR (95%CI)**	**P value**
Age ≥75 years	2.85 (2.51, 3.23)	<0.001	2.08 (1.82, 2.39)	<0.001	1.48 (1.29, 1.71)	<0.001
Female	1.24 (1.10,1.40)	0.001	1.10 (0.97, 1.25)	0.132	1.09 (0.95, 1.26)	0.225
First detection of AF ≥1y	1.21 (1.07, 1.39)	0.003	1.19 (1.05, 1.36)	0.009	1.34 (1.17, 1.53)	<0.001
Obesity (BMI>28kg/m²)	1.00 (0.85, 1.17)	0.991				

Congestive heart failure	3.82 (3.32, 4.41)	<0.001	2.72 (2.34, 3.18)	<0.001	1.86 (1.57, 2.21)	<0.001
Hypertension	1.85 (1.60, 2.13)	<0.001	1.42 (1.22, 1.64)	<0.001	1.24 (1.07, 1.45)	0.006
Diabetes mellitus	1.39 (1.21, 1.59)	<0.001	1.07 (0.93, 1.23)	0.339	1.03 (0.89, 1.20)	0.682
Coronary artery disease	1.90 (1.65, 2.18)	<0.001	1.26 (1.04, 1.53)	0.019	1.15 (0.94, 1.42)	0.174
Peripheral artery disease	1.60 (0.83, 3.08)	0.162				
Valvular heart disease	1.99 (1.68, 2.35)	<0.001	1.01 (0.80, 1.28)	0.916	0.97 (0.76, 1.25)	0.827
PSVT	0.62 (0.37, 1.06)	0.080				

Respiratory diseases	1.87 (1.57, 2.23)	<0.001	1.32 (1.10, 1.58)	0.003	1.34 (1.11, 1.61)	0.002
Drinking	0.75 (0.62, 0.89)	0.001			0.97 (0.79, 1.20)	0.791
Smoking	0.78 (0.65, 0.94)	0.009			1.03 (0.83, 1.28)	0.806
Left atrial diameter ≥ 45 mm	2.62 (2.27, 3.02)	<0.001			1.81 (1.56, 2.10)	<0.001
Ejection fraction ≤ 40%	2.54 (1.82, 3.54)	<0.001			0.79 (0.55, 1.13)	0.197
Antiarrhythmic drug (Sotalol or Propafenone or Amiodarone)	0.45 (0.39, 0.52)	<0.001			0.86 (0.74, 1.01)	0.059

AF ablation	0.13 (0.11, 0.16)	<0.001			0.18 (0.15, 0.22)	<0.001

Abbreviations as in Table-1.

Table-3. Adjusted hazard ratios of adverse clinical outcomes in non-ablated PAF patients with progression, compared with those without progression.

Event	HR (95%CI)	P value
Ischemic stroke/ system embolism	1.52 (1.15, 2.01)	0.003
Cardiovascular hospitalization	1.40 (1.23, 1.58)	<0.001
All-cause mortality	0.92 (0.75, 1.12)	0.391
Cardiovascular death	1.24 (0.94, 1.62)	0.125

Multivariate Cox regression analysis, adjusted by Age ≥75 years, female sex, history of thromboembolism, congestive heart failure, hypertension, diabetes mellitus, coronary artery disease, peripheral artery disease, prescription of oral anticoagulants (NOACs or Warfarin) on admission.