

from around the world

• focus on China

Epidemiology, Risk Factors for Stroke, and Management of Atrial Fibrillation in China

Dayi Hu, MD, FACC, FHRS, Yihong Sun, MD

Heart Center, Peking University People's Hospital, Beijing, China

Throughout the world, atrial fibrillation (AF) is one of the most common arrhythmias seen in daily practice and an important indicator of increased morbidity and mortality. The most serious complication of AF is ischemic stroke, especially in patients with high-risk features (1). However, the available data regarding the incidence of AF and its effect on outcomes are largely from American and European populations. Are these data also valid in today's Chinese AF patient population?

In China, no large-scale epidemiological studies on AF have ever been undertaken, so in 2003 a series of studies were initiated to determine the prevalence and incidence of AF in China and to identify the risk factors for stroke in Chinese AF patients. Due to conflicting results regarding stroke prevention associated with AF in the U.S. and Japan, a randomized clinical trial (RCT) was designed to determine whether warfarin is better than aspirin alone for preventing stroke in moderate- to high-risk Chinese AF patients. The study also sought to determine the utilization of oral anticoagulation therapy among rank-and-file Chinese cardiologists. Such therapy is strongly recommended to prevent thromboembolism in Chinese, U.S., and European guidelines for AF patients, but it is unclear whether this recommendation is being applied in clinical practice across China.

Prevalence of AF in China

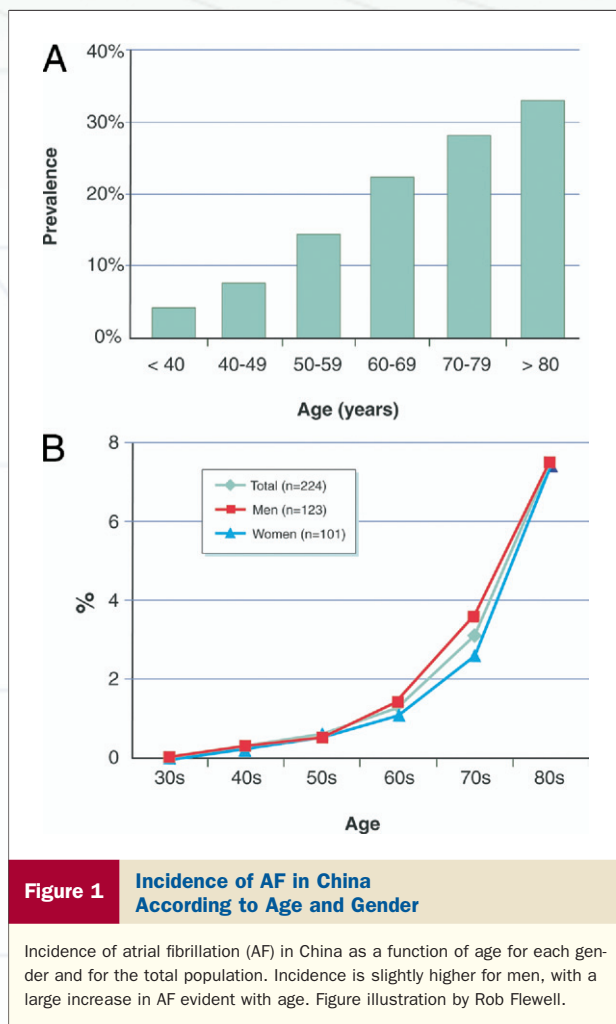
In our first major epidemiological study covering 13 provinces and 14 ethnic groups in China, a total of 29,079 subjects, between the ages of 30 and 85 years, were recruited by means of cluster sampling (2). Every study subject underwent an electrocardiogram (ECG), and 224 cases of AF were identified, including 69 cases (30%) discovered by ECG without previous history or ECG record. This produced a crude AF prevalence rate of 0.77% and an age-adjusted rate of

0.61, suggesting that approximately 8 million adults in China have AF. Like elsewhere in the world, our data indicate that AF in China is more common in the elderly, and the incidence rate is higher for men than for women (0.9% vs. 0.7%, $p = 0.013$) (Fig. 1). The percentages of nonvalvular atrial fibrillation (NVAF), lone AF, and valvular atrial fibrillation (VAF) are 65.2%, 21.9%, and 12.9%, respectively.

We also have evaluated AF in the hospitalized population. A 2003 case-control study included all AF patients consecutively discharged between January 2000 and April 2002 from 18 major Chinese tertiary care centers (3). Among a total of 4,511 hospitalized AF patients, 75.93% had NVAF and 24.07% had VAF. The mean age of NVAF patients was approximately 70 years, with hypertension the most common underlying comorbidity followed by heart failure. In a study by Qi et al. (4) evaluating the admitting diagnoses of 9,297 patients (mean age 65.5 years) from 41 hospitals in China, the diagnosis of AF increased from 7.65% in 1999 to 8.16% in 2001. Overall, the data regarding the prevalence and incidence of AF in the Chinese population are comparable to rates reported in other countries and suggest that the previously observed steady rise in the prevalence of diagnosed AF is continuing in China.

Prevalence of Stroke Related to AF

In both of our previous studies (2,3), we evaluated the prevalence of stroke related to AF. Among the 29,079 patients in our epidemiological study, ischemic stroke was the most common type of stroke, and its incidence was significantly higher in individuals with AF compared with those without AF (12.1% vs. 2.1%, $p < 0.01$) (2). In our case-control study of hospitalized AF patients (3), the prevalence of stroke in non-valvular AF patients was 24.15%, and this rate increased dramatically with age. For example, the



prevalence of stroke was 4.30% in patients younger than 40 years of age and increased to 32.86% among AF patients 80 years of age or older.

By multivariate logistic analysis, age ≥ 75 years, history of hypertension, diabetes, high systolic blood pressure, and

left atrial thrombi were all independently associated with ischemic stroke (3). Another large Chinese retrospective study (9,297 patients from 41 hospitals) confirmed these results with data showing a similar pattern of underlying heart diseases and similar prevalence of stroke (17.5%) in hospitalized AF patients (4). Table 1 summarizes the results of these and other trials.

Anticoagulant Use for Prophylaxis

European and U.S. guidelines recommend antithrombotic therapy to prevent thromboembolism for all patients with AF, except those with lone AF or contraindications, and adjusted-dose oral anticoagulation is more efficacious than aspirin for prevention of stroke in these patients. Moreover, the beneficial effect of the vitamin K antagonist warfarin is achieved with a minimal increase in risk of bleeding complications, namely 1.2% compared with 1.0% for placebo. However, despite convincing clinical evidence, reports show that only 50% of European and American AF patients receive anticoagulant therapy. Is there a similar low rate of anticoagulation use in China?

Based on our epidemiological study, the percentage of AF patients on oral anticoagulation therapy was extremely low—approximately 2.7%—and no patient underwent regular monthly monitoring of international normalized ratio (INR) (2). As for our case-control study of hospitalized AF patients, only 9.1% received anticoagulant treatment (3). More than one-half of the patients (56%) received aspirin, but more than one-third of all AF patients (34.9%) did not receive any prophylactic anticoagulant therapy during hospitalization. Only 6.75% of patients with NVAf and 18.61% of patients with VAF received warfarin.

Among all of the hospitalized NVAf patients, 36.9% (1,121 cases) had at least 2 risk factors, including hypertension, diabetes, age > 75 years, left ventricular ejection frac-

Table 1 Summary of Trials Related to AF

Study (Ref. #), Year	Patients Studied	Definition of AF	Prevalence of AF	Stroke Risk
Zhou et al. (2), 2004	General population	AF by ECG + medical history	0.77%	12.1%
Hu et al. (3), 2003	Hospitalized patients	Nonvalvular AF by medical history	N/A	24.15%
Qi (4), 2005	Hospitalized patients	AF confirmed by medical history	7.9%	17.5%
Sun and Hu (6), 2004	Hospitalized patients	Nonvalvular AF	N/A	24.15%
Hu et al. (7), 2006	RCT	Nonvalvular AF, age < 80 yrs	N/A	Warfarin group 1.8%; aspirin group 4.6%
AF Investigators (8), 1994	Meta-analysis of RCTs	Nonvalvular AF	N/A	Warfarin group 1.4%; control group 4.5%

tion <50%, or ischemic stroke. Based on current guidelines, all of these patients would be candidates for oral anticoagulation therapy. Specifically, European and U.S. guidelines recommend antithrombotic therapy to prevent thromboembolism for all patients with AF, except for 3 situations where aspirin alone (81 to 325 mg/day) is a class I indication: age <60 years and no heart disease (lone AF), age <60 years with heart disease but no risk factors for thromboembolism, or age 60 to 74 years and no risk factors (5). All other patients are considered candidates for oral anticoagulation unless contraindicated.

The rate of anticoagulant treatment was substantially lower in patients older than 75 years. At hospital discharge in China, 2,231 (65.1%) patients received some form of antithrombotic therapy. Independent predictors of receiving warfarin were age (odds ratio [OR] 0.81), coronary heart disease (OR 0.50), heart failure (OR 0.61), and persistent AF (OR 1.88) (6).

Chinese Trial of AF Therapy

In the U.S. and Europe, many RCTs have shown the effectiveness of anticoagulation for preventing stroke in AF patients. However, the data from much of the world suggest that aspirin offers only modest protection against stroke for patients with AF. Yet, a retrospective study by Qi et al. (4) suggested that antiplatelet drug therapy was just as effective as anticoagulant therapy for reducing the incidence of stroke. Therefore, we designed a prospective randomized trial to compare the effects of warfarin versus aspirin for the prevention of stroke in Chinese AF patients.

A total of 828 NVAF patients were randomized to receive either adjusted-dose warfarin (target INR 2.0 to 3.0) or aspirin (150 to 160 mg/day) (7). Average patient age was 63 years, 40% of study participants were women, and the median follow-up was 19 months. The maintenance dose of warfarin was 3.19 ± 0.69 mg, and most of the INR measurements (69.1%) were within the target range. The primary end point of death or ischemic stroke was reduced with warfarin therapy compared with that with aspirin treatment (2.7% vs. 6.0%, $p = 0.03$), for a relative decrease of 56%. The overall thromboembolic event rate was significantly less in the warfarin group compared with the event rate in the group receiving aspirin (5.4% vs. 10.6%, $p = 0.01$) for a relative risk decrease of 52%. There was no significant difference in mortality between the 2 groups.

Warfarin treatment was associated with an increased risk of bleeding compared with aspirin, although the occurrence of major bleeding was low among patients receiving anticoagulant therapy (1.5%). When we combined the end points of death and ischemic or hemorrhagic events, adjusted-dose warfarin remained superior to aspirin (8.4% vs. 13.0%, $p = 0.0047$). Thus, our randomized trial suggests that under optimal monitoring, warfarin (target INR 2.0 to 3.0) is effective and safe for the moderate- to high-risk Chinese patients with AF (7).

Changing Real-World Practice

All of the data above suggest that the prevalence of AF in China is similar to that reported in the Western world. Data from RCTs in the U.S., Europe, and China confirm the efficacy and safety of dose-adjusted warfarin in AF patients (8). However, most of the Chinese AF patients eligible for oral anticoagulant therapy do not receive warfarin as recommended in applicable Chinese guidelines. Thus, the data underscore a huge gap in China between clinical practice and guideline recommendations regarding the prevention of stroke due to AF.

The low rate of anticoagulant therapy for AF patients in China may be due to concerns regarding excess bleeding related to the narrow safety window of the vitamin K antagonist warfarin and the need for frequent dose adjustment to maintain optimal INR. Yet this concern does not seem to influence the clinical practice of those physicians with patients on anticoagulation therapy, given the fact that none of the patients appear to be followed regularly to check INRs and make dose adjustments, if necessary. This is a serious deficiency in medical practice, given evidence from our randomized study indicating that the risk of stroke or peripheral thromboembolism rose steeply with an INR <1.5, while an INR ≥ 3.0 was an independent risk factor for hemorrhage (6). Interestingly, contrary to usual belief, our case-control study with hospitalized AF patients showed that patients experiencing hemorrhage were not significantly older than those without this complication (3).

If concerns regarding excess bleeding and the belief that treatment with vitamin K antagonists is costly and time-consuming both contribute to the hesitation many clinicians show in prescribing warfarin, even for patients at a high risk for stroke, how do we change clinical practice in China? First, education is certainly necessary to increase the awareness of Chinese cardiologists in terms of the high inci-

dence of stroke due to AF and the efficacy of preventing stroke in AF patients. Secondly, newer oral anticoagulants (e.g., oral thrombin inhibitors or Xa inhibitors) may help to facilitate the use of anticoagulant treatment for AF. However, before these new drugs are available commercially, warfarin is still the best and only choice for moderate- to high-risk AF patients in the prevention of any thromboembolism, if the rank-and-file Chinese cardiologists decide to prescribe it.

To improve the management of anticoagulant therapy in AF patients, especially in high-risk patients, numerous methods have been reported to be useful in the American and European health care setting. These include the establishment of specialized anticoagulation clinics, point-of-care patient self-testing, and computerized algorithms for warfarin dose adjustment (9). Therefore, our third and final recommendation is a greater effort to promote the systematic follow-up of AF patients, and to facilitate this effort, we support the development of special clinics to assist in the care of these patients in China.

Conclusions

A series of studies in mainland China suggested an AF prevalence of 0.77%, which increased significantly with age. The incidence of stroke is significantly higher among individuals with AF, and independent risk factors for stroke include age ≥ 75 years, history of hypertension, presence of diabetes, high systolic blood pressure, and left atrial thrombi. While prophylaxis with warfarin significantly reduces the primary end points of death and ischemic stroke in Chinese patients with AF, use of oral anticoagulation is extremely low in China, both in the general AF population and among hospitalized patients. Like much of the rest of

the world, China faces problems managing a growing population of patients with AF, including a huge gulf between clinical guidelines and real-world practice. Immediate steps are necessary to promote the prophylaxis of thromboembolism in China.

REFERENCES

1. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham study. *Stroke* 1991;22:983–8.
2. Zhou Z, Hu D, Chen J, et al. An epidemiological survey of atrial fibrillation in China. *Chin J Intern Med* 2004;43:491–4.
3. Hu D, Sun Y, Zhou Z. Risk factors for stroke in Chinese with non valvular atrial fibrillation: a case-control study. *Chin J Intern Med* 2003;42:157–61.
4. Qi W-H, Society of Cardiology, Chinese Medical Association. Retrospective investigation of hospitalised patients with atrial fibrillation in mainland China. *Int J Cardiol* 2005;105:283–7.
5. Fuster V, Ryden LE, Cannon DS, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation). *J Am Coll Cardiol* 2006;48:e149–246.
6. Sun Y, Hu D. The efficiency and safety of anticoagulation therapy in atrial fibrillation in Chinese. *Chin J Intern Med* 2004;43:258–60.
7. Hu D, Zhang H, Sun Y, et al. The randomized study of efficiency and safety of antithrombic therapy in nonvalvular atrial fibrillation: warfarin compared with aspirin. *Chin J Cardiol* 2006;34:295–8.
8. AF Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. *Arch Intern Med* 1994; 154:1449–57.
9. Hirsh J, Fuster V, Ansell J, Halperin JL. American Heart Association/American College of Cardiology Foundation guide to warfarin therapy. *J Am Coll Cardiol* 2003;41:1633–52.

Key Words: anticoagulation ■ atrial fibrillation ■ epidemiology ■ stroke.

doi:10.1016/j.jacc.2008.05.042