

Antithrombotic Treatment of Atrial Fibrillation in China

Dayi Hu MD, FACC, FHRS
Yihong Sun MD

Atrial fibrillation (AF) is a common arrhythmia encountered in daily clinical practice in China. It is also one of the most important risk factors to increased morbidity and mortality. The most serious complication associated with AF is ischemic stroke, which may occur in 5–15% of patients with high risk features. ^[1]Anticoagulant therapy is of proven benefit in stroke reduction and is recommended in established guidelines.^[2]

The prevalence and treatment of AF in China has been unknown for quite a long time. Therefore, we performed series of studies in mainland china to identify the epidemiology and risk factors of stroke in AF patients. Furthermore, one RCT trial were designed to establish anticoagulation with warfarin as the optimal prophylaxis for moderate to high risk AF patients, compared with aspirin.

Prevalence of atrial fibrillation

Atrial fibrillation is common, especially with the aging of the population. Totally, 14 natural populations representative of different areas of the country were chosen to perform an epidemiology study which was mainly on AF. The crude rate of prevalence of AF in China is 0.77 %, significantly increased with age. AF is more common in men than in women (0.9 % vs 0.7 %, $P = 0.013$). Among all the cases, valvular AF, nonvalvular AF and lone AF were 12.9 %, 65.2 % and 21.9 % respectively. Ischemic stroke was the most frequent type and the stroke rate among cases with AF was significantly higher than those without (12.1% vs 2.1%, $P < 0.01$). However, most patients (98%) did not receive prophylaxis anticoagulation and no more than 40 percent of the patients received aspirin. The prevalence of diagnosed AF in Chinese population is comparable with rates found in other primary care studies and emphasizes that the previously observed steady rise in the prevalence of diagnosed AF is continuing.^[3]

Risk of stroke and anticoagulation in real-life

Several studies, largely performed in the western hemisphere, have established that atrial fibrillation (AF) is an independent risk factor for stroke with an overall risk of ischemic stroke in patients with AF averaging approximately 5% per year. There are scarce studies of stroke risk factor profiles for the Chinese atrial fibrillation population. In a large retrospective study from Chinese population, Dr. Qi reported that the prevalence of stroke was 17.5% in the hospitalized patients. ^[4]

Our retrospective study included the patients consecutively discharged from 18 tertiary care centers selected to provide representation of all sections of the Chinese population, between January 2000 and April 2002. The results demonstrated that hypertension is the most common underlying disease, followed by heart failure. The prevalence of stroke in nonvalvular AF patients is 24.15%. In multivariate logistic analysis, age \geq 75, history of hypertension, diabetes, high systolic blood pressure, LA thrombi were independently associated with stroke. ^[5]In this cohort of hospitalized patients, 2231 (65.1%) patients received antithrombotic therapy at discharge. However, only 9.1% received anticoagulation treatment. More than half of the patients (56%) received aspirin and still another one third did not receive any prophylaxis therapy. In the population epidemiology investigation, the rate of oral anticoagulation is extremely low, approximately 2% of all, and no one underwent regular monitoring of INR.

The low anticoagulation rate may be due to the concern about hemorrhage. The case control study showed the patients with hemorrhage is no significantly older than those without complications. INR \geq 3.0 is an independent risk factor for hemorrhage. The risk of stroke or thromboembolism rose steeply with INR below 1.5. ^[6]To achieve optimal anticoagulation in patients with AF, values of INR below 1.5 and above 3.0 should be avoided. But, some of the retrospective study showed that antiplatelet drug is just as same effective as anticoagulant, these merit randomized clinical trials.

RCT for the prevention of stroke : dose-adjusted warfarin (INR 2-3) compared with aspirin

Many randomized trials have shown the effectiveness of anti-coagulation in preventing stroke in patients with AF. In a pooled analysis the Atrial Fibrillation Investigators found that warfarin significantly reduced the risk from 4.5% per year to 1.45% per year, a relative risk reduction of 68%.^[7] The beneficial effect of warfarin was achieved with minimal increase in risk for bleeding complications 1.2% compared with 1.0% for placebo. Despite convincing clinical evidence, reports from western world showed that 50% of patients with AF receive antithrombotic therapies.

It is unknown if similar results exist in Chinese population. The prospective randomized study is required to indentify the effects of warfarin compared to aspirin on the prevention of stroke in Chinese AF patients. We randomized 704 non-valvular AF patients to receive either adjusted-dose warfarin (traget INR 2-3) or asiprin (150-160mg/d). Average patient age were 63.26±9.97 years , 40% were woman. The median follow-up period is 19 months. The maintain dose of wafarin was 3.19±0.69 mg by average, with most of INR (69.1%) in the target range. The primary end point of death or ischemic stroke was reduced by warfarin, as compared with aspirin (2.7% vs 6.0%, p=0.03), with the relative risk decreased by 56%. The thromboembolism events in aspirin group were significantly higher than that in warfarin group(5.4% vs 10.6%, P=0.01) with the relative risk decreased by 52%. There was no significant difference of the mortality between the two groups. The combined end points were statistically decreased by adjusted-dose warfarin (8.4% vs13.0% , P =0.0047). Warfarin treatment was associated with increased risk of bleeding compared to aspirin, although the occurrence of major bleeding is low (1.5%). Under intense monitoring, warfarin is effective and safe for the moderate to high-risk atrial fibrillation patients in China^[8]

Fill the gap between practice and guideline

All the data above suggested the prevalence of AF is tremendous in China, the same as western world. Randomized control trial confirmed the efficacy and safety of warfarin in AF patients.

However, most of the patients eligible for oral anticoagulant did not received warfarin according to the guidelines. There is a great gap between practice and guidelines in the prevention of stroke in China.

Today, the only way to administer OAC is as vitamin K antagonists. This treatment involves regular and well-managed controls of the international normalized ratio with frequent dose adjustments. The treatment is complicated by many food and drug interactions. Treatment with vitamin K antagonists is thus costly and time consuming both for the patients and their healthcare providers. These drawbacks contribute to the hesitation to recommend routine prescription of OAC even to patients with high risks.

To improve the management of anticoagulation in AF patients, especially high risk patients, the following methods were reported useful: Special anticoagulation clinic, Point-of-Care Patient Self-Testing and Computerized Algorithms for Warfarin Dose Adjustment.^[9] The education is another key point for doctors and patients to recognize the importance of prophylaxis therapy on stroke.

The upcoming new OAC treatments, eg, oral thrombin inhibitors or Xa inhibitors, are highly warranted to facilitate the use of routine OAC treatment in AF. Before new drugs are available, warfarin is still the best choice for moderate to high risk AF patients in the prevention of thromboembolism.

REFERENCE

1. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: The Framingham Study. *Stroke* 1991;22:983-988
2. Fuster V, Ryden LE, Cannom DS, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines; European Society of Cardiology Committee for Practice Guidelines; European Heart Rhythm Association; ACC/AHA/ESC 2006 Guidelines for

The 2nd ISHNE Atrial Fibrillation Worldwide Internet Symposium

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. *Circulation*. 2006 Aug 15; 114(7): e257-354.

3. Zhou ziqiang, Hu Dayi , Chen Jie ,et al. An epidemiological survey of atrial fibrillation in China. *Chin J Intern Med* , 2004, 43(7),491-494

4. Wen-Hang QI; Society of Cardiology, Chinese Medical Association. Retrospective investigation of hospitalised patients with atrial fibrillation in mainland China. *Int J Cardiol*. 2005 Dec 7;105(3):283-7.

5. Hu Dayi, Sun Yihong, Zhou Ziqiang. Risk factors for stroke in Chinese with non valvular atrial fibrillation :a case-control study, *Chin J Intern Med* , 2003,42(3):157-161

6. Sun Yihong ,HU Dayi.The efficiency and safety of anticoagulation therapy in atrial fibrillation in Chinese. *Chin J Intern Med* , 2004,43(4),258-260

7.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;154:1449-1457.

8.Hu Da-yi, Zhang He-ping, Sun Yihong, et al. The randomized study of efficiency and safety of antithrombotic therapy in nonvalvular atrial fibrillation: warfarin compared with aspirin. *Chin J Cardiol*, 2006;34(4):295-298

9.Hirsh J, Fuster V, Ansell J, Halperin JL; American Heart Association/American College of Cardiology Foundation. American Heart Association/American College of Cardiology Foundation guide to warfarin therapy. *J Am Coll Cardiol*. 2003;41(9):1633-52.