

The Optimal Treatment For Atrial Fibrillation In Less Developed Countries

Xiaohan Fan, Shu Zhang

State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100037, People's Republic of China.

Abstract

Atrial fibrillation (AF) is the most common arrhythmia and is a major cardiovascular challenge due to its close association with increased morbidity and mortality. Although the incidence and prevalence of AF is slightly lower in developing countries than in developed countries, the AF-associated risk of stroke is similar. Treatment of AF is far from satisfactory in developing countries, which may be due to limited health-care resources and social and racial characteristics that differ from Western populations. Chronic rate control is still the main treatment strategy of persistent AF because anti-arrhythmic drugs have only a modest long-term effect on maintenance of sinus rhythm, and no superior impact in terms of cardiovascular outcomes. With the development of ablation techniques and strategies, more AF patients received catheter ablation, although the benefit, complications, and high recurrence rate associated with AF ablation remain under investigation. Improvement in antithrombotic therapy of AF has been observed, although still fewer patients receive oral anticoagulants in developing countries than in Western countries. Novel treatment for the prevention of thromboembolism, such as new oral anticoagulants with different mechanisms of action or the percutaneous transcatheter closure of the left atrial appendage, has recently been introduced in developing countries as an alternative option for the prevention of AF-associated strokes. More data are needed regarding upstream therapy.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia, with an estimated prevalence of 2% of the general population in the developed world.¹⁻³ AF is a major cardiovascular challenge due to its close association with high risk of stroke, incidence of congestive heart failure, and high mortality. Current mainstay therapy for AF includes assessment of thromboembolic risk and stroke prevention, applying appropriate rate-control or rhythm-control strategies, and management of associated diseases.⁴ Because AF becomes more prevalent with age, the prevalence of AF is estimated to increase progressively in the future.

The prevalence of AF varied among developing countries as well as in community- or hospital-based studies. AF is also associated with many co-morbid cardiovascular diseases, such as hypertension,

heart failure, and diabetes. Treatment of AF is far from satisfactory in developing countries, which may be due to limited health-care resources and different social and racial characteristics from Western populations. Therefore, this review summarises the prevalence, current state of catheter ablation, rate or rhythm control strategy, and antithrombotic treatment of AF in less developed countries.

Epidemiology Of Atrial Fibrillation

The prevalence of AF has been reported ranging from 0.5% to 2%^{1-3,5} in Western countries. According to previous studies, the incidence of AF increases with age and is more prevalent in men than women.^{6,7} Current data indicate that the prevalence of AF in developing countries is slightly lower than in developed countries. In general population, the prevalence of AF was 0.67% in Tanzania,⁸ 0.7% in Korea,⁹ 0.77% in China,¹⁰ 1.1% in Taiwan,¹¹ and 1.2% in India.¹² In some developed countries, the prevalence of AF ranged from 1.6% in Japan,¹³ 3.6% in America¹⁴ and 4% in Australia.¹⁵ However, it is difficult to compare the prevalence of AF among different countries because the study population might be different in age, and may have co-morbid cardiovascular diseases. A recent review showed similar prevalence of AF in developing countries to that reported in some developed countries.¹⁶

The presence of co-morbid diseases can affect AF patients' prognosis, their risk of stroke, their risk of haemorrhage with the use of anticoagulation therapy, and the choice of anti-arrhythmic drugs. Therefore, AF-associated cardiovascular diseases, such as hypertension, heart failure, and diabetes, should be identified in AF patients. Hypertension, the most frequent condition associated with

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Corresponding Author:

Shu Zhang
State Key Laboratory of Cardiovascular Disease,
Clinical EP Lab and Arrhythmia Center,
Fuwai Hospital,
National Center for Cardiovascular Diseases,
Chinese Academy of Medical Sciences and Peking Union Medical College,
Beijing, 100037,
People's Republic of China.

Table 1: Atrial fibrillation catheter ablation 2012

	Japan	China	South Korea	Taiwan	India	Singapore
AF ablation procedures	21000	12343	1561	450	500	82
AF ablation centres	350	331	30	No data	20	2
Ablation physicians	875	2000	No data		25	15
AF ablation rate per million inhabitants	133.4	7.4	25.5	16.7		

AF, Atrial fibrillation. Data from APHRS white book 2013

AF, ranged from 40% in Malaysian patients¹⁷ to 40.3% in Chinese patients,¹⁸ to 71.9% in Turkish AF patients.¹⁹ Although valvular heart disease is more common in the developing countries than in the West, the ratio of valvular AF was 18.7% in men and 31.2% in women in China,²⁰ which was similar to other racial AF patients (26.7%).²¹ Prevalence of other co-morbid cardiovascular diseases in AF patients also varied greatly among countries. In China, AF-associated diseases were reported, including 12.3% ischemic heart disease, 33.1% heart failure, 17.7% diabetes, and 6.9% hyperthyroidism.¹⁸ In Malaysia, the prevalence of ischemic heart disease was 42.5%,¹⁷ and heart failure prevalence was 56% in South Africa.²²

Current Status Of Treatment Of AF

Rate Or Rhythm Control

Current guidelines⁴ recommend target ventricular rate (VR) control to improve hemodynamic status and relieve symptoms for the majority of patients with persistent AF. Emergency cardioversion should be the initial therapeutic approach for AF patients with hemodynamic instability due to very rapid VR and/or underlying structural heart diseases. When restoration of sinus rhythm is not possible or is not attempted in patients with permanent AF, drugs blocking AV nodal conduction should be used to achieve rate control both at rest and during exercise. For patients with paroxysmal AF, catheter ablation (complete pulmonary vein isolation) is recommended as an alternative to anti-arrhythmic drug therapy (Class I A indication) for patients with symptomatic recurrent paroxysmal AF on anti-arrhythmic drug therapy in an experienced centre. Anti-arrhythmic drug therapy is also reasonable in AF patients without structural or coronary heart disease when the agent is well tolerated.

In developing countries, the use of rate or rhythm control strategies might be different from that in developed countries. In a retrospective analysis of 9,297 hospitalized AF patients from 41 hospitals in China,¹⁸ paroxysmal AF was treated mainly by rhythm control (pharmacological cardioversion: 56.4%), whereas only 18.2% patients with paroxysmal AF received VR control. The majority of patients with persistent AF (82.8%) received VR control treatment with digoxin, β -blockers, and calcium antagonists. It is worth noting that few patients received electrical cardioversion, and 23.9% patients with paroxysmal AF and 13% patients with persistent AF were untreated. The RealiseAF registry study²¹ included 10,523 AF patients worldwide, and found 57.5% of all patients receiving VR control strategy and 37.2% patients with rhythm control treatment, and AF was controlled in 59.0% of the 9665 patients and not controlled in 41.0%. Among the patients controlled, 26.5% were in sinus rhythm and 32.5% were in AF with heart rate \leq 80 bpm. In regard to anti-AF drugs in less developed countries, amiodarone (64%) is still the most commonly used anti-arrhythmic drug for preventing the recurrence of AF. Although the efficacy of sotalol in the prevention of recurrence of AF is similar to that of propafenone and equal to that of amiodarone in converting atrial fibrillation to sinus rhythm,²³ only

few AF patients received sotalol for rhythm control treatment.¹⁸ The use of propafenone is also less common because it is limited in AF patients without underlying structural heart diseases. Dronedronone is a “new” anti-AF drug, which has not been used in China and some other developing countries. For VR control during AF, the generally used drugs are digoxin, beta blockers, or nondihydropyridine calcium channel blockers.¹⁸

Catheter Ablation Therapy

Catheter ablation of AF has become a widely accepted procedure in most of the large cardiac centres worldwide. In the last decade, great increase in procedures of catheter ablation for AF was observed in less developed countries. Data from the APHRS white book show an increasing trend in ablation procedures across some Asia Pacific countries and regions: Japan, China mainland, Korea, and Taiwan.²⁴ Across the four countries and regions with available data for 2011–2012 (Table 1), a large gap in AF ablation rate per million inhabitants is observed between developed country Japan (133.4) and other less developed countries and regions, with 25.5 in Korea, 7.3 in Taiwan and 7.4 in China mainland. Japan is also the country with the highest ratio of AF/total ablations (44.7%), whereas the lowest AF ablation ratio is in Taiwan (5.3%), and it is 22.6% in Korea, 13.9% in China mainland, and 0 in Philippines. At present, multiple approaches have been developed for catheter ablation of AF. Data from registration study of AF catheter ablation in China²⁵ showed that paroxysmal AF was the main indication (71.5%), and circumferential pulmonary vein isolation (CPVI) is currently the major ablation type in China (60.2%). Other AF ablation strategies used in China include CPVI plus necessary atrial auxiliary line (20.1%), stepwise ablation (13.9%), CPVI plus fractionated atrial electrogram ablation (10.4%), fractionated atrial electrogram ablation (0.5%), and segmental PVI (0.5%). During a mean of 9.6 ± 3.8 months follow-up, the success rate was 82.1%, and 17.9% patients had recurrent AF. The complication rate was as low as 1.7%. Factors impacting success and recurrence rate are similar between developing and developed countries, including left atrium diameter, type of AF, age, and experiences of ablation doctors. Few patients with recurrent AF after catheter ablation had undergone an attempt at surgical ablation. Cryoballoon-based PVI is a recently developed technique for the treatment of AF with acceptable mid-term results in terms of the success and safety.²⁶ Recent studies also showed that the long-term outcomes after cryoballoon PVI are similar to those reported for radiofrequency ablation.^{27,28} Some cryoballoon-based PVI procedures have been performed in some large electrophysiology (EP) centres in China.

Cryoballoon-based ablation might be a promising strategy for management of AF in intermediate centres of cardiology.

Antithrombotic Treatment

AF And Stroke

The high risk of mortality and stroke in patients with AF are relatively consistent among reports from the Western population and

Asia Pacific region. The Framingham study reported that patients with AF have a two-fold higher risk of mortality and five-fold higher risk of stroke compared with controls.^{7,29} The risk of mortality and stroke for patients with AF was found to be 2.23 and 3.87 in Taiwan.¹¹ The annual risk of ischemic stroke in patients with nonvalvular AF seems to be higher in Chinese (9.28%)³⁰ than in Western populations (5%).³¹ Prevalence of stroke in patients with AF was similar in less developed countries: 10.7% to 22.8% in China, 23% to 27% in Pakistan, 17.6% in Brazil, and 17.4% in Cameroon.¹⁶

Current Status Of Antithrombotic Treatment In Less Developed Countries

The reported utilization of anticoagulant and antiplatelet varied greatly among studies due to differences in studied population or period. Data from the Global AF registry showed that the use of oral anticoagulants (OACs) in patients with CHADS₂ scores ≥ 2 was lower in Asian countries compared with Western countries. A recent analysis from the RE-LY trial also showed that the use of OACs among patients with a CHADS₂ score of ≥ 2 was greatest in North America (65.7%) but was only 11.2% in China.³² The rate of anticoagulant use was consistently low in other less developed countries, such as Malaysia (16%) Moldova (7.1%), and Kosovo (27%).¹⁶ Antiplatelets (mostly aspirin) were highly prescribed in China (from 34.1% to 94.3%), Kosovo (72%), Turkey (55.6%), Argentina (63%), etc.¹⁶ Additionally low rates were reported in studies in Malaysia (8%), Zimbabwe (10%), Brazil (19.9%-21.2%), and South Africa (23%).¹⁶ Even for hospitalized patients with AF in China,¹⁸ the rate of antithrombotic treatment was only 64.5%, and 35.5% patients did not receive any antithrombotic treatment. Antiplatelet agents were used in 57.9% of hospitalized patients with AF, and the use of warfarin was only 6.6%.¹⁸ The general lacking of a standard anticoagulation clinical practice, the low patient compliance rate, and the concerns of cost are well-recognized plausible causes of the limited utilization of warfarin in this patient population.

In regard to preventing stroke and thromboembolic events in patients with AF, warfarin is the most potent conventional anticoagulation drug, superior to aspirin and clopidogrel,³³ with an acceptable increase in severe haemorrhagic event rate. Standard intensity (INR 2-3) is effective and safe for stroke or bleeding events in European subjects.³⁴ Even in developed countries, INR was poorly controlled in 30% to 92% of patients on anticoagulants.¹⁶ In less developed countries, the proportion of patients with therapeutic anticoagulation with warfarin, measured using the INR, was approximately 30%-50%: 39.1% to 40% in China, 51.7% to 53.6% in Bosnia and Herzegovina, 50.1% in Brazil, 47.7% in Turkey, 32.6% in India, and 28.5% in Moldova.¹⁶ The controversy about the efficacy and safety of low intensity of INR (1.5-2.0) in Asians was once discussed 10 years ago.^{35,36} Although few studies in Chinese indicate that the low intensity of INR (range 1.6 to 2.0) is a reasonable anticoagulation intensity for patients with nonvalvular AF,³⁷ especially for octogenarians patients with nonvalvular AF (>80 years old),³⁸ these data should be cautiously interpreted due to sufficient evidence for standard intensity.

Current AF guidelines have recommended the use of risk schemes for stroke and thromboembolism (CHA₂DS₂-VASc) and bleeding risk assessments in AF patients.³⁹ In China, use of stroke risk stratification schemes is inadequate in clinical practice. Together with the less antithrombotic therapy, less warfarin treatment, and less regular monitoring of INR in Chinese patients with AF, great

improvements are needed for optimal antithrombotic therapy in China.

The Use Of New Anticoagulation Therapy

Recently, two classes of new oral anticoagulant drugs are being developed for stroke prevention in AF-- oral direct thrombin inhibitors and oral factor Xa inhibitors. New oral anticoagulants do not require such intensive monitoring or complex dose adjustment as warfarin and have been approved for stroke prevention in AF in many developed countries.³⁹⁻⁴¹ Although some less developed countries have approved dabigatran for anticoagulation therapy in AF patients,^{42,43} few data are available for the usage of new oral anticoagulants in developing countries. Except for some potential issues encountered by new oral anticoagulants, such as potential complications, use in patients with renal disease, and lack of specific antidotes, the high costs of new oral anticoagulants might be a big problem for their use widely in less developed countries.

Racial Difference

Previous study has observed a racial difference in ischemic stroke rates between whites and Asians.⁴⁴ There is also a racial difference in rates of intracranial haemorrhage while on warfarin. Intracranial haemorrhage rates are significantly higher in nonwhites (Blacks, Hispanics, and Asians) than whites in patients receiving warfarin.⁴⁵ Various factors may contribute to the bleeding risk with anticoagulant therapy in Asian patients. First, less monitoring of INR due to noncompliance, food, and drug interactions can contribute to an excess bleeding risk. Second, different ethnic prevalence of gene polymorphisms can lead to different warfarin dose requirements between racial groups.⁴⁶ In addition, there might be a racial difference in intensity of warfarin therapy between Asians and whites.^{37,47} In regards to racial differences in pharmacokinetic parameters of NOACs, the population pharmacokinetic analysis of dabigatran in patients from RE-LY trial showed that the AUC at steady state is increased by 25.5% in South Asians compared with other ethnicities.⁴⁸ However, the effect of this magnitude seems not to be of clinical relevance. The subgroup analysis of RE-LY trial confirmed that haemorrhagic stroke rates are higher on warfarin in Asians versus non-Asians.⁴⁹ However, dabigatran significantly reduced haemorrhagic stroke in both Asians and non-Asians. It seems that there was no racial difference in the haemorrhagic stroke rates on dabigatran, but a racial difference on warfarin. In addition, no data support racial differences on apixaban, rivaroxaban, and edoxaban.

Other Therapies

Because blood clots arise from the left atrial appendage (LAA) in most cases with atrial fibrillation, the percutaneous closure of the LAA might be a promising alternative for the treatment of patients with AF at a high risk of stroke, in whom long-term anticoagulation therapy is not possible or not desired. WATCHMAN and Amplatzer™ Cardiac Plug are the two mostly implanted devices worldwide with good clinical results.^{50,51} In China, a new self-expanding LAA occluder (Lifetech LAmbré™ device) has been evaluated in animal studies and multicentre clinical trials.^{52,53} LAmbré consists of an umbrella and a cover connected by a short central waist, is delivered by an 8-10 French sheath, and has full recapture and repositioning capabilities. We are expecting data on the efficacy and safety of this new device.⁵⁴

Current guidelines⁴ recommend co-prescribing an angiotensin receptor blocker (ARB) or an angiotensin-converting enzyme inhibitor (ACEI) with an anti-arrhythmic drug as upstream

therapy to increase the likelihood of maintaining sinus rhythm after cardioversion.

Upstream therapy with statins is also associated with a decreased risk of recurrence in patients with persistent AF after electrical cardioversion.⁵⁵ A randomized trial performed in Chinese patients with lone paroxysmal AF suggests that the combination of perindopril or losartan with low-dose amiodarone is more effective than low-dose amiodarone alone for the prevention of AF recurrence. Left atrial enlargement can also be inhibited by adding losartan or perindopril to amiodarone.⁵⁶ However, there are limited studies about upstream therapy in China.

Conclusion:

AF is a major cardiovascular challenge in modern society, and the impact of this disease on the risk of stroke and mortality is similar between developed and less developed countries. AF-associated risk factors and comorbidities should be identified and treated because the presence of co-morbid diseases can affect the prognosis of patients with AF. Rate control remains the main strategy, whereas catheter ablation is becoming more prevalent as the first-line therapy for paroxysmal AF in a few large hospitals in less developed countries. Both the rate of anticoagulant treatment and the use of stroke risk stratification schemes are relatively inadequate in less developed countries. Prophylactic antithrombotic treatment with OACs should be improved in the future. Few data are available on the use of new oral anticoagulants, percutaneous closure of the LAA, and upstream therapy in developing countries. Optimal treatment of AF remains challenging in less developed countries.

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