

Contemporary oral anticoagulant therapy of patients with atrial fibrillation in China: Status, obstacles, and strategies for improvement

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SUMMARY Atrial fibrillation (AF) and subsequent stroke and death have become major public health problems in China. Oral anticoagulant (OAC) forms the backbone of prevention of AF-related stroke. However, the quality of OAC use in AF patients in China is not clear. The focus of this narrative review is to summarize the current status of OAC therapy in China and compare it with the studies conducted internationally. In general, most data of OAC use in China were reported around 10-50%, with an increasing proportion of high-risk patients receiving OACs, however, still much lower than those in other countries and regions. Moreover, the phenomenon of inappropriate OAC prescribing and poor long-term persistence and adherence with OAC therapy in AF patients in China have also been noted. The 1-year adherence and persistence of OACs are as low as 50%. Multiple factors from the physicians, patients, and OAC drugs contribute to these phenomena. The management of OACs in AF patients in China needs to be further improved by the joint efforts of healthcare administration (policy makers) and health systems including medical associations, hospitals, and physicians.

Keywords atrial fibrillation, oral anticoagulation, stroke, temporal trends, China.

1. Introduction

Atrial fibrillation (AF) is the most prevalent arrhythmia in clinical practice (1). It is well known that one of the major hazards of AF is the significantly increased risk of ischemic stroke, disability, and mortality (2). Hence, stroke prevention is central in the management of AF.

Oral anticoagulation (OAC) therapy, involving the use of vitamin K antagonists (VKA, mostly warfarin) and non-VKA oral anticoagulants (NOAC), could reduce thromboembolic events and improve prognosis in patients with AF who have a high stroke risk. Currently, OAC therapy is recommended as a standard treatment for stroke prevention by international guidelines for AF (3-5). However, OAC usage is inconsistent on the global and national levels. Although numerous data on OAC use in AF patients in China have been published, a systematic overview and discussion are still lacking. In the present review, we intend to summarize the contemporary OAC use for patients with AF in China and compare it with the studies conducted internationally to help identify which aspects need refining. We also analyzed potential causes

of the deficiencies, and explored improvement strategies. Furthermore, we present some recommendations on OAC management during the COVID-19 pandemic.

2. Burden of AF in China

With the aging trends in global population, the incidence and prevalence of AF are increasing (6). The Global Burden of Diseases study in 204 countries found that in 2019, there were about 59.7 million (95% uncertainty interval: 45.7 to 75.3 million) prevalent cases of AF and atrial flutter, nearly doubled to the prevalent cases in 1990 (Figure 1A) (7). The problem seems to be even worse in China. On one hand, the rapid aging of the population and the increased industrialization and urbanization have resulted in a rapid increase in the prevalence and absolute number of patients with AF in China (Table 1). Two community-based studies showed the weighted prevalence rates of 0.65% (8) and 0.77% (9) for AF in Chinese adults nearly twenty years ago. A subsequent data from the China Hypertension Survey Group found that prevalence of AF in the

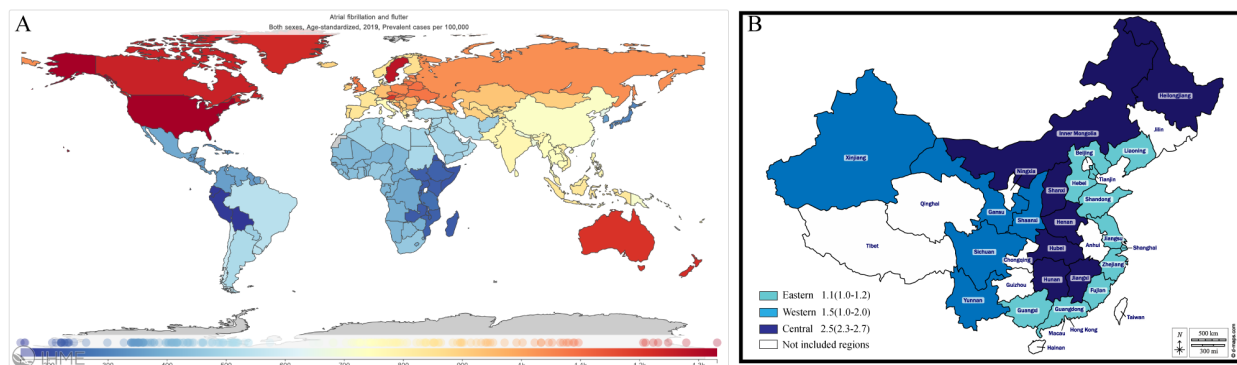


Figure 1. The map of age-standardized AF prevalence in the world (1A) and China (1B). Data in panel A are derived from GBD 2019, and are presented as cases of AF per 100,000 population in both sexes (available from <http://vizhub.healthdata.org/gbd-compare>); data in panel B are from the latest national epidemiology survey of China (Data from Shi S, et al. Lancet Reg Health West Pac. 2022, 11;23:100439. Map data is copyrighted and available from https://d-maps.com/carte.php?num_car=17503).

Table 1. Overview of the prevalence of AF in the general population of China

First author	Period	Population (age in years)	Sample size	Age	Male (%)	Num. of AF	Prevalence of AF	Ref.
Zhou Z	2003	Adult (≥ 30)	29,079	52.5 \pm 22.4	46.6	224	0.65	(8)
Li Y	2004	Adult (≥ 35)	19,363	NA	44.6	199	0.77	(9)
Wang Z	2012	Adult (≥ 35)	31,230	52 (51 - 53)	50.0	357	0.71	(10)
Du X	2014 to 2016	Adult (≥ 45)	47,841	NA	NA	932	1.8	(11)
Shi S	2020 to 2021	Adult (≥ 18)	114,039	55 \pm 17	47.9	2,604	1.6	(12)

Abbreviations: AF, atrial fibrillation; Num., number; Ref., reference; NA, not available.

Chinese population above 35 years of age was 0.71% (10). A national survey of middle-aged and older adults conducted between 2014 and 2016 indicated the weighted AF prevalence was 1.8% (11). A most recent epidemiological survey showed that the prevalence of AF in Chinese adults was 1.6% (Figure 1B), and it is estimated that currently approximately 20 million patients have AF in China, which is significantly higher than previously reported and the estimation (12). We anticipate that with an aging population, the growing trend in the causes of AF (such as ischemic heart disease), and the higher detection of AF with advanced technology and screening, the healthcare burden of AF will continue to increase in China.

On the other hand, AF-related stroke is becoming an alarmingly increasing burden on the national healthcare system. Based on data from medical insurance database, the incidence of AF-related stroke has increased by more than 13-fold in the southwest of China from 2001 to 2012 (13). Another study from Hong Kong illustrated a 2.5-fold increase of AF-related stroke and transient ischemic attack over a 15-year period in Chinese populations, affecting all age groups and mostly non-anticoagulated patients (14). Thus, more effort is needed to improve health care for AF in China.

3. OAC use in patients with AF in China

In general, epidemiological studies investigating OAC use in patients with AF in China have been uneven. Few nationally representative surveys have been conducted,

and provincial-level studies are often conducted in economically developed regions. The vast majority of studies showed that the proportion of patients with AF prescribed OACs ranged from 10% to 50% in China, which is much lower than that in European and American countries and many Asian countries such as Japan and South Korea (15-18). These data provide deep insight into current practice and opportunities for quality improvement in AF management.

3.1. Unsatisfied OAC use in hospital-based studies

Early nationwide, multicenter studies were mostly subgroups of global registries, as listed in Table 2. Two large-scale, worldwide, prospective registries of AF, including Global Anticoagulant Registry in the Field-Atrial Fibrillation (GARFIELD-AF) and Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation (GLORIA-AF) cohort have both shed light on the lowest OAC use in China compared with other countries or regions (Figure 2) (15,17-19). Among the cohorts, OAC therapy was administered to only 20% to 30% of patients in China, which was paralleled by up to 80% usage in patients from Japan. Gratifyingly, follow up studies identified promising trends in OAC use for AF in China (Figure 3). Two latter national investigations, performed in 2012 and 2014, respectively, showed that OAC use had increased to 31.7% and 43.7% in AF patients in China (20,21). The most recent data from the China AF Center (which involved 362 hospitals and is the

Table 2. The OAC use in patients with AF from multicenter or international studies in China

First author	Data source	Period	Study location	Numbers of patients	OAC use	Ref.
Sun Y	GARFIELD-AF	Dec 2009 to Oct 2011	29 tertiary hospitals	805 NVAF	28.7%	(19)
Huisman MV	GLORIA-AF Phase I	May 2011 to Jan 2013	NA	713 NVAF	20.3%	(17)
Mazurek M	GLORIA-AF Phase II	Nov 2011 to Dec 2014	NA	1,018 NVAF	21.0%	(15)
Sun Y	China Registry of Atrial Fibrillation	Jul 2012 to Dec 2012	111 hospitals	3,562 NVAF and 599 VAF	31.7%	(20)
Guo Y	ChiOTEAF registry	Oct 2014 to Dec 2018	44 hospitals	6,420 AF	43.7%	(21)
Zhao QY	China AF Center	Nov 2017 to Oct 2018	362 tertiary hospitals	137,181 AF	64.8%	(22)

Abbreviations: OAC, oral anticoagulation; NVAF, non-valvular atrial fibrillation; AF, atrial fibrillation; Ref., reference; GARFIELD, Global Anticoagulant Registry in the Field-Atrial Fibrillation; GLORIA-AF, Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation; NA, not available; ChiOTEAF, Optimal Thromboprophylaxis in Elderly Chinese Patients with Atrial Fibrillation.

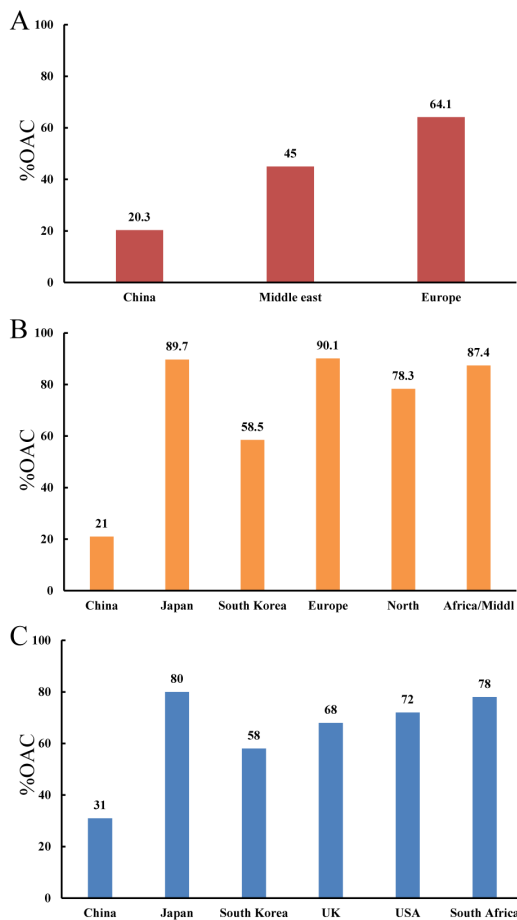


Figure 2. The OAC use in patients with AF in China compared with other countries or regions. Data in panel A are derived from GLORIA-AF Phase I; data in panel B are from GLORIA-AF Phase II; data in panel C are from GARFIELD-AF.

largest sample size analyzed to date) demonstrated that among 137,181 hospitalized patients with AF in reporting information systems from November 2017 to October 2018, two-thirds had a CHA₂DS₂-VASc score of ≥ 2 , 79.1% (72,176/91,246) of whom were treated with OAC (22). However, the data from the China AF Center were manually entered and collected only from tertiary general medical centers; these might have led to an overestimation of the true OAC use in AF patients in China.

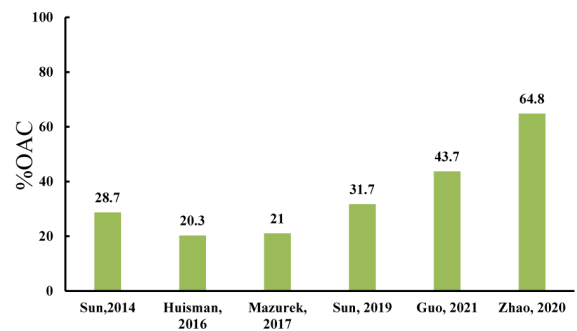


Figure 3. Secular trends of OAC use in patients with AF in China. The OAC use gradually increased in national studies over time.

Regarding regional studies from different provinces, widespread but extremely variable OAC underuse for AF could be observed. However, it is gradually improving. As early as 2006, there have been reports of only 18.2% of high-risk patients with NVAF on OAC medication in Beijing, the capital city of China (23). Two registry-based studies thereafter indicated that the use of OAC in patients with AF admitted into tertiary hospitals in Beijing increased from 35% in 2011 to 49% in 2015 (24). Similarly, a recent report on the medical insurance database covering up to 30 million people in Shanghai, the most developed city in China, showed a substantial increase in OAC use among patients with AF, in which more than half (56.57%) were taking OAC in 2020, compared to 19.46% in 2015 (25). Two cross-sectional survey studies conducted in 2013 and 2018, respectively, showed OAC use of inpatients with NVAF had increased from 11.5% to 36.2% in Chongqing area (26,27).

In addition, the presence of OAC underuse in AF patients with ischemic stroke has also been noted. OAC therapy should be made mandatory in these patients in the absence of contraindications according to the current guidelines. Approximately ten years ago, there were reports of a 20% of OAC use in patients with AF-associated stroke in northwestern China (28). In another study from Beijing, this rate was reported to be 40% in patients with NVAF within 3 months of new-onset acute stroke (29). Similarly, the use of OAC in stroke patients with AF and/or rheumatic heart disease at discharge

increased between 2010 and 2011 and 2016 and 2017 (26.4% to 45.1%, P for trend < 0.001) in West China Hospital, one of the top comprehensive hospitals in China (30). Data from the most authoritative survey data source of China Stroke Center Alliance, involving 35,767 patients from 1,430 hospitals, showed OAC use was almost double in the five years from 2015 to 2019 (pre-hospital: 14.3% to 21.1%, at discharge: 23.2% to 47.1%) (31).

It appears from the above studies (either national or regional) that although OAC use has gradually increased over time in China, it has remained less than satisfactory. Another notable fact is that most previous studies focused exclusively on patients in tertiary-grade hospitals. Further research is needed on OAC use in patients with AF in hospitals at the lower end of the distribution and economically underdeveloped areas.

3.2. Gross OAC underuse in population- or community-based samples

Although OAC undertreatment was found in hospital-based studies in China, it is important to acknowledge this problem is not limited to that. Typically, the OAC intake rate of in-hospital patients is often higher than that of patients in the community. In fact, statistics have shown more serious OAC underuse in population-based studies in China.

Data from the China National Stroke Screening Survey, collected between 2013 and 2014, a representative nationwide sample of 1,252,703 individuals showed that as low as 2.2% of AF patients with stroke were taking OAC medication (32). Two later large-scale AF epidemiology surveys found that 4.1% and 6.0% of high-risk patients with AF received OAC, respectively (33,34). This situation is also not optimistic even in economically developed regions. A cross-sectional survey conducted in rural Shanghai in 2015 showed that 5.9% of patients with AF were on warfarin, while up to 61.1% were off any antithrombotic medication (35). In another community-based study recently conducted in Shanghai in 2017, Chen *et al.* (36) found that the OAC use had risen to 20%. Thus, the lack of awareness and undertreatment of community patients is already a serious public health problem in China that needs to be addressed using a whole-of-system approach.

3.3. Temporal trends of OAC prescription patterns

For almost a decade, the change in the OAC use away from VKA towards NOACs for thromboembolic prevention in AF worldwide is evident from studies across various countries (15,37). However, NOACs use varied substantially across countries because of the different timing of approval and variations in the attitudes of physicians/patients. In 2017, about 86.1% to 93.1% of patients with AF initiated on NOACs in Europe

and the United States through electronic health records or administrative claims databases (38). The Fushimi AF Registry indicated NOACs overtook warfarin in 2016 in Japan (39). In China, NOAC use has increased rapidly in parallel with global trends and became the most common OAC in 2019, 3-7 years later than other main countries. Through the database of the Hospital Prescription Analysis Corporation Program of China, the prescription of NOACs has rapidly increased in visits and costs in five major, well-developed economic cities (Beijing, Shanghai, Hangzhou, Guangzhou, and Chengdu) from 2012 to 2019 (40, 41). And that the defined daily doses of rivaroxaban exceeded those of warfarin in patients with NVAF since 2019 (42). Similarly, data from the China Stroke Center Alliance also showed that the combined use of dabigatran and rivaroxaban exceeded the use of warfarin for AF patients with stroke in the third quarter of 2019 (31). In fact, the costs of NOACs decreased markedly after they were included in the National Health Insurance in 2017 and had similar cost-effectiveness to warfarin in patients with NVAF (42). The overall use rate of OAC has increased in China, partly driven by an increase in the availability of NOACs.

Although it is evident from time-series analyses that the OAC use in patients with AF in China is consistently gradually improving. However, these studies also showed that overall OAC use remained suboptimal and that there is still much room for improvement. Further concerted and comprehensive efforts by society as a whole are needed to improve the quantity and quality of OAC therapy for patients with AF in China.

4. Other roadblocks to high-quality OAC usage in China

It should be emphasized that the use of OAC is the first step in preventing ischemic stroke in patients with AF. In clinical practice, however, other issues also remain. In addition to low OAC use, the presence of inappropriate OAC prescribing and poor adherence and persistence with OAC therapy in AF patients in China have also been noted.

4.1. High prevalence of inappropriate OAC prescribing

A reasonable dose of OAC can maximize its effect and reduce adverse events. However, studies have shown that less than 50% of patients on OAC medication were prescribed with appropriate OAC in China according to the recommended guidelines. In an early analysis of the China National Stroke Registry, among 96 NVAF patients with stroke who were taking warfarin, only one was admitted with an international normalized ratio between 2 and 3 (43). A later multicenter study conducted in Xinjiang province showed that up to 86.3% and 3.3% of patients with a CHA₂DS₂-VASc score ≥ 2 received insufficient and excessive OAC,

respectively (44). Two recent single-center studies from Fuwai Yunnan Cardiovascular Hospital and West China Hospital reported the prevalence of inappropriate OAC prescription was 46.3% and 56.1% in 2020, respectively (45,46). By contrast, the rate of inappropriate OAC prescription was found to be 13.7% to 26.3% in elderly Japanese AF patients from ANAFIE Registry (47), and 17% in AF patients from Swiss-AF and BEAT-AF registers (48).

Despite the magnitude of the problem, research in this field is not active in China. To uncover the frequency and factors that may contribute to inappropriate NOACs use, two ongoing, national, multicenter studies were investigating real-world data on the rationality of NOACs prescription in AF patients in China (49,50). The results of these studies are keenly awaited and will be of importance in guiding rational OAC therapy in Chinese patients.

4.2. Poor adherence and persistence with OAC therapy in Chinese patients

The optimal benefit of OAC therapy requires good medication-taking behavior. Both non-adherence and non-persistence of OAC are associated with increased stroke risk in patients with AF. Long-term adherence and persistence with OAC therapy are global challenges (51). However, significant area disparities were observed. Although studies investigated the adherence and persistence of OAC in patients with AF in China are few with small sample sizes. The published data revealed a relatively lower adherence and persistence to OAC among AF patients in China compared with American, Western European, and major Asian cities (Figure 4) (16,52-54). In addition, during the literature review, we found a noteworthy issue in that many of the studies from China conflated the concepts of "adherence" and "persistence". Indeed, adherence or compliance refers to patients actually taking the prescribed medication, while persistence or continuation indicates a patient staying on therapy, regardless of drug dosing and schedule (55).

A recent meta-analysis showed that 1 in 3 patients with AF adhered to NOAC < 80% of the time at the

global scale, whereas the good adherence rate at 1 year can be up to 90% in many Western countries (54). One study involving 315 patients with AF in 11 hospitals across China showed that adherence (defined as the mean proportion of days covered ≥ 0.80) declined steadily to 73.7% after the first month after admission and 36.4% in the 10-month follow-up (56).

Data from several studies conducted in Beijing showed a considerable variation in the proportion of OAC persistence (57-59). In one study, only 40.4% of patients who received warfarin completed the first repeat prescription within 3 months (57). Similar findings have been reported in another multicenter study, in which 44.4% of NVAF patients discontinued warfarin within one year (58). However, researchers of the China-AF Registry reported that the 3-year persistence to warfarin and NOACs were 87.2% and 81.3% over a similar period, respectively (59). The authors believed that the China-AF Registry was created by cardiologists; therefore, patients enrolled in this registry could have actively or passively gained knowledge about OAC.

5. Potential reasons for unsatisfactory OAC therapy in China

Multiple possible factors (Figure 5) may be responsible for the unsatisfactory use of OAC in China. First, the gaps in medical technical level and service quality in this middle-income country compared to Western countries cannot be ignored. Second, the difficulty in detecting AF and screening universal high-risk populations influences the awareness and further treatment of patients with AF. Third, OAC use in patients with a known AF may be influenced by several physician-, patient-, and drug-related factors such as physician specialization, patient health literacy, and patient economic status (Table 3).

5.1. Physician-related factors

Physicians' knowledge of anticoagulation and correct assessment of thromboembolic risk in AF patients is the premise of OAC therapy. However, multiple studies have shown that Chinese doctors' knowledge of OAC is

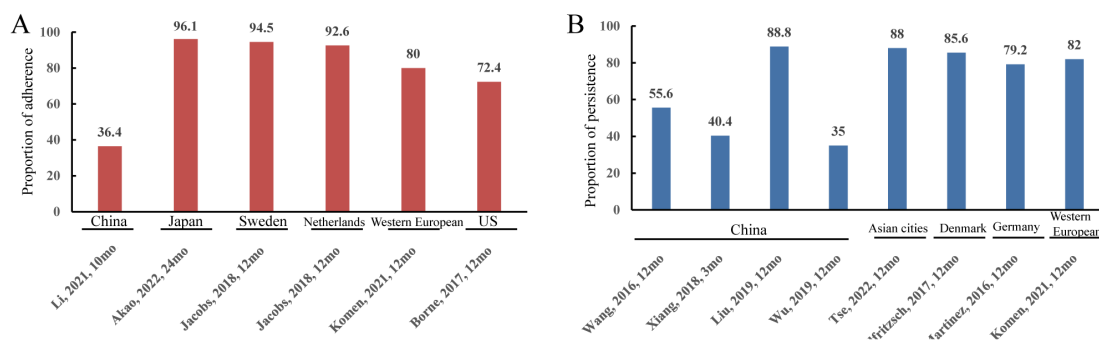


Figure 4. The proportion of adherence (4A) and persistence (4B) to OAC therapy of AF patients in China compared with other countries or regions.

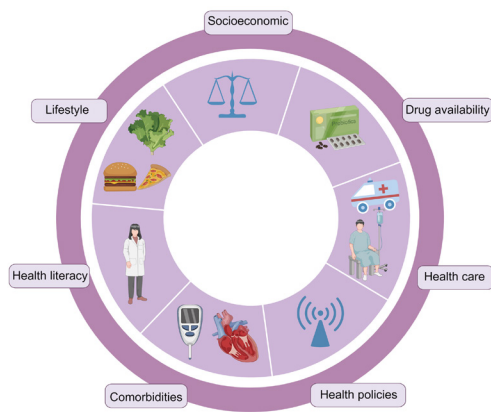


Figure 5. Illustration of the multifactorial etiology of OAC underuse in China. Although there is overlap among these factors, their co-existence induces unsatisfactory OAC therapy in China.

Table 3. Common factors associated with suboptimal OAC use in AF patients in China

Physician-related factors	
Medical services vary markedly by hospitals	
Lack of knowledge about oral anticoagulants among doctors	
Synchronization of previous experience with evolving guidelines	
Insufficient focus on the quality of OAC therapy	
Patient-related factors	
Unaware of AF-related stroke risk	
Medication concerns	
Multiple comorbidities	
Elderly	
Lower health literacy	
Low socioeconomic status	
Drug-related factors	
Drug price, costs and availability	
Health policy on OAC drugs	
Multiple medication	

Abbreviations: OAC, oral anticoagulation; AF, atrial fibrillation.

insufficient and that there are huge gaps between regions, hospitals, and departments, which suggests opportunities for improvement at the hospital level.

A national survey of Chinese doctors showed approximately 70% of emergency physicians and general practitioners were unfamiliar with the CHA₂DS₂-VASc score, while cardiologists and clinical pharmacists performed better (60). Another survey of neurologists in Hubei Province showed that education level, professional title, working years, hospital grade, and hospital location influenced doctors' knowledge of AF and the options for OAC (61,62). Several studies performed in different areas, such as Shanghai (63), Guangdong (64), and western provinces (65), reported similar results: up to 80% of doctors in primary hospitals or communities had insufficient knowledge of OAC use for patients with AF. It seems that grassroots physicians are the weak link in the management of AF in China. Therefore, it is necessary to improve the practice of primary care medicine.

In addition, possessing knowledge does not translate into action. Based on data from the Improving Care

for Cardiovascular Disease in China (CCC)-Atrial Fibrillation (AF) project, the proportion of hospitalized patients with NVAf who underwent embolization risk assessment increased from 16.2% in the first quarter of 2015 to 67.1% in the fourth quarter of 2019 ($P < 0.001$) in tertiary hospitals in China (66). This suggests that the evaluation of thromboembolism risk in patients with AF is not ideal, even in a batch of top hospitals in China. There is a need for more training on anticoagulant therapy and for clinicians to standardize their clinical practice.

5.2. Patient-related factors

Patient cognition and preferences are important reasons for the initiation, adherence, and persistence of OAC therapy. A cross-sectional survey conducted in the People's Hospital of Henan Province showed that 32.6% and 15.6% of patients with AF passively forgot and voluntarily discontinued warfarin, respectively (67). The concerns arising from the belief that OAC therapy is harmful are important reasons for non-adherence to OAC (67). A cohort study from five hospitals in China showed that 66.3% of the patients discontinued OAC between 3 and 14 months after AF ablation because of concerns over the risk of bleeding (68). A discrete choice experiment investigated the attribute preference for OAC therapy in patients with AF from Beijing and Shenzhen, and the results showed that patients were most concerned about the risks of myocardial infarction, stroke, and major bleeding (69). These findings reflect concerns about the possible adverse health effects of OAC. Therefore, it is necessary to educate patients with AF on the efficacy and safety of anticoagulation therapy to encourage them to adhere to OAC therapy.

In addition to intrinsic patient factors such as health literacy and knowledge regarding AF, many clinical patient-level factors could also influence OAC therapy in patients with AF. Several studies have investigated the characteristics of patients who did not take, adhere to, or persist with OAC therapy (31,46,70-73). Common patient factors integrated from the findings of previous studies were older age, non-urban residence, lower education level, lower income, history of stroke, multiple comorbidities, and antiplatelet therapy (14). In fact, it is important to note that the risk factors for poor compliance to OAC in AF patients in China were usually not the same as those in patients from other countries. For example, older patients often had better adherence and persistence to OAC therapy in other countries (74), but not in China. Therefore, we should focus on identifying the risk factors and characteristics associated with OAC adherence and persistence in Chinese patients, which may be helpful in identifying patients with non-adherence and non-persistence. The next step is to translate these findings into incentives to help patients take OAC appropriately.

5.3. Drug-related factors

Compared with warfarin, NOACs have the advantages of having a rapid onset of action, no need for unnecessary routine coagulation monitoring, no dosage adjustment, and fewer food-drug interactions. The long-term persistence of NOACs is better than that of warfarin (75). However, domestic studies have shown that the rate of discontinuation of NOACs was higher than that of warfarin in AF patients in China (59,76). According to a questionnaire survey from the China-AF registry, dabigatran therapy in patients with NVAF was associated with no improvement in satisfaction and a higher discontinuation rate compared with warfarin therapy, which was thought to be largely due to the increased economic burden of NOACs (176.78 ± 9.15 vs. 2.49 ± 0.76 USD/month, $P < 0.001$) (77). Indeed, the level of NOACs use also partly depends on government subsidies. However, with the patent expired status of many NOACs, the costs of China's generic drugs have markedly dropped, and we speculate that circumstances might change and drug costs would no longer be a decisive factor governing the use of NOACs. Further studies on this topic are required. In addition, studies have shown that other drug-related factors, such as dosing frequency, affect OAC use and deserve attention.

6. Strategies to improve OAC therapy in AF patients in China

How can we overcome these obstacles? We believe that the collaboration of our healthcare administration, medical associations, hospitals, and physicians is needed to promote OAC use in AF patients in China and further improve the overall prognosis of patients with AF in China (Table 4).

6.1. Measures from the government departments

In fact, the government can do much to ameliorate the reality of OAC underuse in AF patients in China; first of all, they could reduce the economic burden on

patients. In 2019, the Chinese government launched a centralized medicine procurement policy together with the resident medical insurance reimbursement policy for chronic diseases, both of which substantially reduced the price and improved the cost-effectiveness of drugs (78). A cost-benefit analysis showed that NOACs have comparable and even better cost-effectiveness than warfarin in Chinese patients with NVAF since the inclusion of NOACs in the catalog of medication reimbursement (42,79). A welcome fact is that there has been an increase in overall OAC prescriptions since NOACs became available in China (80). At present, dabigatran and rivaroxaban have entered the fifth batch of national centralized drug procurement, and it is expected that implementing low central government prices would benefit more patients with AF.

Second, most published data regarding OAC use in AF patients in China were obtained from hospital digital information systems or community sampling surveys, although there have been a small number of reports using regional medical insurance databases (81). In contrast, many national cardiovascular registries in other countries are widely used to improve the quality of healthcare services, assess the effectiveness and safety of new therapies, and conduct research (82). Thus, we suggest that the national medical insurance database and medicine agency monitoring data be developed and made open access to facilitate better evaluation of the actual OAC usage in China, which will lead to the proposal of new strategies (83).

Third, quality control should be further strengthened through medical administration. Currently, the National Health Commission of China has formulated five management indicators for admitted patients with AF: the evaluation rates of stroke and bleeding risk, the rate of OAC use in patients with valvular and non-valvular AF, and the incidence of complications during left atrial appendage closure (84). It is hoped that national-level interventions will be more effective than calls from doctors and that medical institutions will continue to improve the OAC management of patients with AF.

Fourth, the Ministry of Health of China established

Table 4. Strategies to combat poor OAC use of patients with AF in China

Topic	Strategies	Scope/Location
Poor knowledge of AF patients	<ol style="list-style-type: none"> 1. Improving residents' health literacy. 2. Promoting patient education campaigns on AF and OAC. 3. More convenient tools such as multimedia, electronic communications, and networking technology. 	<p>Government, public policies. Hospitals and physicians. Government, public policies, related enterprises, physicians.</p>
Insufficient capacity of physicians	<ol style="list-style-type: none"> 1. Promotion and introduction of the AF guideline. 2. Build hierarchical diagnosis and treatment system. 3. More home-grown clinical trials to offer more clinical evidence. 	<p>Medical associations and large hospitals. Government, medical associations, and hospitals. Medical associations and hospitals.</p>
High cost of NOACs	<ol style="list-style-type: none"> 1. When the patent expires, the drug price decreases through competition with generic drugs. 2. NOACs include in medical insurance reimbursement. 	<p>Pharmaceutical companies in China. Government and national health insurance system.</p>

Abbreviations: OAC, oral anticoagulation; AF, atrial fibrillation; NOAC, non-vitamin K antagonist oral anticoagulant.

a hierarchical diagnosis and treatment system for AF management. We hope that the efficiency of AF therapy can be improved through this hierarchical system. The form of "up and down assistance" is supported by tertiary hospitals and participated in by secondary hospitals and community hospitals, which enables grassroots patients with AF to obtain homogeneous, standardized, and efficient management. However, the establishment of the AF management system in such a large setting is a lengthy and challenging process and requires the cooperation of specialist cardiologists, pharmacist teams, and community general practitioners. Several top hospitals have established integrated management models based on local characteristics (85). These hospitals have developed a local network for sharing clinical decision making; they have used the alliance platform to link the management of AF in top and primary hospitals, which is worthy of widespread promotion.

In addition, the government should support regular AF screening for those at high risk of AF in the context of an aging population and support original research on anticoagulation therapy in the Chinese population. We strongly believe that these administrative interventions under China's unique medical model may have distinct advantages in improving the quality of OAC use in patients with AF.

6.2. Measures from the cardiovascular medical associations

The dedicated efforts of many cardiologists have greatly improved anticoagulation therapy in AF patients in China. Experts formed the Atrial Fibrillation Center Union of China (AFCUC), which created the China Atrial Fibrillation Day (June 6th) and developed a flurry of activities such as advocating for education of inhabitants on AF and helping with the construction of the AF management system. Nevertheless, additional efforts are needed to maintain and further improve OAC use in AF patients in China.

First, studies have shown that doctors in primary and community hospitals and non-cardiologists, such as emergency department physicians, are the weak link in the management of AF. However, these doctors are in close contact with patients with AF. Therefore, it is necessary to guide and train these medical staff to improve their knowledge and strengthen their management capacity. We believe that the goal of medical associations and top hospitals is by no means solely to foster experienced electrophysiologists. Training primary healthcare physicians will be driven by medical associations, such as AFCUC, so that the primary healthcare facilities can strengthen their gatekeeper role.

Second, most of the studies cited in the current AF guidelines of China were conducted abroad. Management strategies and guidelines for AF need to be modified using data obtained from Chinese patients. However,

single-center studies have often provided inadequate clinical evidence. Hence, medical associations should prompt high-quality, multicenter clinical research to fill the evidence gap for OAC therapy in AF patients in China, such as the comparison of the clinical net benefit of different NOACs and the efficacy and safety of OAC therapy in high bleeding risk groups, the elderly, and other special populations.

Third, medical associations should launch more quality improvement programs, such as the CCC-AF project (86). A major strength of medical associations is that they can recruit hospitals to participate in one program to improve the quality of national medical care. Such projects will involve collection of clinical information from patients with AF, analysis, feedback, and process improvement to eventually help guide the development of the national health quality improvement system (86).

Overall, medical associations should leverage this strength to achieve the most impact in this area of national health. The associations could provide detailed national information and discover the gaps and barriers to effective OAC use in AF patients in China, which is valuable for better OAC usage across China and to explore more reasonable management pathways suitable for the national conditions in China (87).

6.3. Measures from the hospitals and physicians

Medical treatment can be characterized by a series of interactions between patients and doctors. The first step in solving current problems is recognizing that collaboration must occur between health care practitioners and patients. Poor knowledge about AF and OAC among patients with AF is associated with adverse cardiovascular events (88). Educating patients is an essential part of the clinical management of AF. Propagating and educating patients about their disease conditions and about the efficacy, and advantages and disadvantages of OAC use during outpatient visits, hospitalization, and after discharge is an important basis for improving drug compliance and fostering mutual trust between physicians and patients. An international cluster-randomized trial conducted in developing countries showed that a multifaceted educational intervention could increase the proportion of patients with AF treated with OACs (89).

Growing evidence-based research findings support the Atrial Fibrillation Better Care (ABC) pathway as a structured approach for the management of AF, endorsed in the 2020 European Society of Cardiology guidelines (3,90,91). In fact, the ABC pathway emphasizes the importance of integrated care, which requires a multidisciplinary team (from specialists to caregivers) in AF management. First, patient participation should be encouraged in the process of deciding whether anticoagulation should be used as this can improve

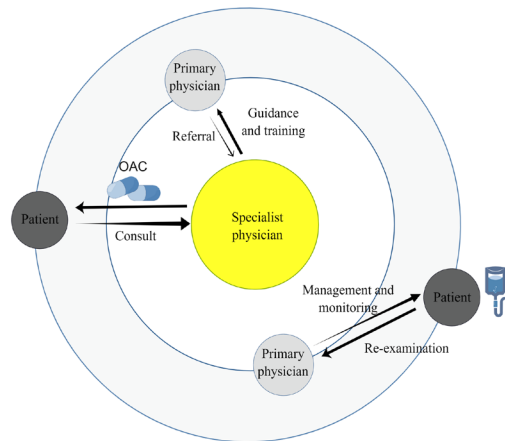


Figure 6. A central-radiation model for OAC therapy in AF patients in China. Specialist physician in the center and doctors in peripheral hospitals should assume corresponding responsibilities to better communicate with patients and improve their OAC use.

patient understanding, trust, satisfaction, and OAC compliance (92). Secondly, clinical pharmacists can assist clinicians in prescribing rational doses of OAC and avoiding adverse drug interactions. Studies from Shanghai (93) and Chongqing (94) showed that patients' OAC compliance can be improved through comprehensive evaluation and medication education by clinical pharmacists and physicians. Therefore, for some qualified top hospitals, clinical pharmacists should be encouraged to participate in OAC treatment and the whole-process management of patients with AF (Figure 6). Third, with the development of modern technology, many medical tools such as mobile phone software have been developed. A pilot study developed a WeChat mini-program integrating decision support and patient follow-up, which was shown to improve medication compliance and satisfaction in patients with AF (95). The mobile Atrial Fibrillation App trialed managed patients with AF using mobile phone software that integrates clinical decision support, health education, patient participation, and structured follow-up. The results showed that mobile health management can improve patients' disease cognition, medication adherence, quality of life, anticoagulation satisfaction (96), and long-term outcomes (97). In addition, another computer-assisted platform was also shown to improve the medical compliance of patients with AF (98). However, more efficient and easy-to-accept management platforms should be explored to improve OAC compliance in patients with AF. We also hope that artificial intelligence-assisted tools could help doctors in primary care to manage patients with AF (99).

To conclude, the integrated care approach to AF management is not only for prompting OAC use but also for improving patient prognosis and reducing the risk of mortality and hospitalization. This requires consistent efforts and the involvement of the medical team.

Education and changing ideas in health care need to be increased in hospitals and physicians in China.

7. Management of OACs during the COVID-19 pandemic

Today, the global epidemic situation remains sobering, and China is no exception. The increase of AF-related mortality during the COVID-19 pandemic in US has been observed (100). Several issues should be taken into consideration in order to protect AF patients in China. First, the epidemic has reduced the frequency of patients seeking medical treatment, especially those in grassroots areas and far from hospitals. Thus, it is necessary to encourage primary physicians to be responsible for the OAC management and follow-up visit. Second, NOACs is especially suitable during the epidemic since it does not require frequent blood monitoring. Third, personalized smartphone Apps with user-friendly design that involve medical professionals are needed for improving antithrombotic therapy safety.

8. Summary and perspective

AF-related stroke incurs a heavy burden to patients, doctors, and the healthcare system in China. Over the past two decades, clinical management of AF has gradually improved in China through updates in AF management guidelines, various practice incentives, the introduction of NOACs, and the strong marketing of biopharmaceutical manufacturers. However, at present, OAC therapy in AF patients in China is far from ideal, with obstacles such as low OAC use, frequent inappropriate dose prescription of OAC drugs, and poor long-term medication adherence and persistence in patients with AF. We have come a long way, but we know that there is yet far to go.

Our present review highlights important gaps in the current clinical management of AF patients in China, which has important implications for healthcare policy making to achieve the Healthy China 2030 goal. Overall, these aspects are timely and thought-provoking. The information may provide further insights for more effective surveillance of AF and stroke prevention for improved clinical outcomes. Joint efforts of the government and medical communities are needed to minimize the burden of stroke and death caused by poor OAC use, adherence, and persistence.

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