Time Trends of Aspirin and Warfarin Use on Stroke and Bleeding Events in Chinese Patients With New-Onset Atrial Fibrillation

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BACKGROUND: Much of the clinical epidemiology and treatment patterns for patients with atrial fibrillation (AF) are derived from Western populations. Limited data are available on antithrombotic therapy use over time and its impact on the stroke or bleeding events in newly diagnosed Chinese patients with AF. The present study investigates time trends in warfarin and aspirin use in China in relation to stroke and bleeding events in a Chinese population.

METHODS: We used a medical insurance database involving > 10 million individuals for the years 2001 to 2012 in Yunnan, a southwestern province of China, and performed time-trend analysis on those with newly diagnosed AF. Cox proportional hazards time-varying exposures were used to determine the risk of stroke or bleeding events associated with antithrombotic therapy among patients with AF.

RESULTS: Among the randomly sampled 471,446 participants, there were 1,237 patients with AF, including 921 newly diagnosed with AF, thus providing 4,859 person-years of experience (62% men; mean attained age, 70 years). The overall rate of antithrombotic therapy was 37.7% (347 of 921 patients), with 4.1% (38 of 921) on warfarin and 32.3% (298 of 921) on aspirin. Antithrombotic therapy was not related to stroke/bleeding risk scores (CHADS₂ [congestive heart failure, hypertension, age $\geq$ 75 years, diabetes, stroke (doubled)] score, $P = .522$; CHA₂DS₂-VASc [congestive heart failure, hypertension, age $\geq$ 75 years (doubled), diabetes mellitus, stroke or transient ischemic attack (doubled), vascular disease, age 65 to 74 years, and female sex] score, $P = .957$; HAS-BLED [hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly (> 65 years), drugs/alcohol concomitantly] score, $P = .095$). The use of antithrombotic drugs (mainly aspirin) increased in both women and men over time, with the rate of aspirin increasing from 4.0% in 2007 to 46.1% in 2012 in the former, and from 7.7% in 2007 to 61.9% in 2012 in the latter (P for trend for both, $< .005$). In the overall cohort, the annual stroke rate was approximately 6% and the annual major bleeding rate was about 1%. Compared with nonantithrombotic therapy, the hazard ratio for ischemic stroke was 0.68 (95% CI, 0.39-1.18) for aspirin and 1.39 (0.54-3.59) for warfarin.

CONCLUSIONS: Aspirin use increased among Chinese patients newly diagnosed with AF, with no relationship to the patient's stroke or bleeding risk. Warfarin use was very low. Given the health-care burden of AF and its complications, our study has major implications for health-care systems in non-Western countries, given the global burden of this common arrhythmia.

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ABBREVIATIONS: AF = atrial fibrillation; CHADS₂ = congestive heart failure, hypertension, age $\geq$ 75 years, diabetes, stroke (doubled); CHA₂DS₂-VASc = congestive heart failure, hypertension, age $\geq$ 75 years

(doubled), diabetes, stroke or transient ischemic attack (doubled), vascular disease, age 65 to 74 years, and female sex; HAS-BLED = hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly (> 65 years), drugs/alcohol concomitantly; HR = hazard ratio; ICD-9 = *International Classification*

The prevalence and incidence of atrial fibrillation (AF) are increasing globally, which is having a profound impact on patient disability and mortality.¹ The most serious, common complication of AF is thromboembolism (TE), and AF-related stroke is associated with a 30-day mortality of 24%. Thus, thromboprophylaxis with oral anticoagulation is strongly recommended for patients with AF who have one or more stroke risk factors.

For nearly 50 years, vitamin K antagonists (eg, warfarin) have been used as oral anticoagulants for stroke prevention in AF. Overall prevalence of warfarin treatment was 55% in patients with AF who had a CHADS₂ (congestive heart failure, hypertension, age $\geq$ 75 years, diabetes, stroke [doubled]) score > 1 in the United States,² and 80% among European cardiology practices.^{2,3} Indeed, warfarin use has been increasing in Western countries. For example, in a Minnesota community-based study, warfarin use increased from 9% from 1980 to 1984 to 30% in the period from 1995 to 2000, as did aspirin use (from 18% to 52%); these were associated with a reduction in stroke by 3.4% per year.⁴ Some of the various limitations of warfarin have been overcome by the introduction of non-vitamin K antagonist oral anticoagulants (NOACs) (eg, dabigatran, rivaroxaban, apixaban), given their approvals in North America and Europe for stroke prevention in patients with AF.

However, in most Asian countries, suboptimal thromboprophylaxis in AF is still common.⁵ In a Japanese cohort with AF, the rates of warfarin and antiplatelet agent use were 48% and 31%, respectively, while the rate of stroke, transient ischemic attack (TIA), or systemic TE was as high as 22%.⁶ Our previous hospital-based study found that only 14% of patients in a Chinese cohort with AF were receiving warfarin and 60% were taking aspirin, while the rates of stroke or systemic TE and the bleeding events in a 2-year period were 8% and 5%, respectively.⁷

Although there are substantial data on antithrombotic management in Western populations,⁸ the information on AF epidemiology and antithrombotic management over time in Asian countries is limited. Limited data are available on antithrombotic therapy use over time and its impact on the stroke or bleeding events in Chinese patients newly diagnosed with AF.

To address this issue, first we studied time trends of antithrombotic therapy with relation to stroke and bleeding events in Chinese patients with new-onset AF during an 11-year period (2001 to 2012), using a large medical insurance database including > 10 million people. Second, the impact of antithrombotic therapy on stroke and bleeding risk was evaluated in this real-world Chinese population with AF. Third, a comparison was made with published data from Western countries.

Materials and Methods

Database Description

The medical insurance database in the Yunnan Province, China, from January 1, 2001, through December 30, 2012, was used. This database includes > 10 million individuals who enrolled in a large, governmental

medical insurance plan. This medical insurance scheme covers urban residents in Yunnan Province, located in the far southwest of China, spanning approximately 394,000 km² and with a population of 46.3 million (2011 population statistics), representing 3% of the total Chinese population.

Inclusion of individuals entering the medical insurance plan allows us to report on medical events and provide evidence of the diagnosis and treatment of various medical conditions to the Center for Medical Insurance, for the medical care services to be paid by the government. Thus, the diagnoses of events are based on clearly certified validated records that the patients attended the hospital. Also, all participants have a permanent personal registration number through which every medical event could be identified and information on medical history, drugs, and mortality could be recorded. Thus, the baseline data plus the follow-up data of every medical event could be identified over the observational period.

Sampling Method

The subjects have been continually entered into the governmental medical insurance plan since 2001. The medical insurance data were compiled in Oracle RDBMS 10g (Oracle Corporation). Structured Query Language and systematic sampling using randomization blocks enabled random sampling of the study population.

To achieve a representative sample reflecting longitudinal changes, the individuals in the medical plan were stated by calendar year. Then, a 5% sample of medical insurance data was selected randomly. Thus, a total of 1,228,639 people were selected. After excluding those with incomplete data ($n = 2,611$ cases) and readmission ($n = 754,582$), 471,446 cases

of Diseases, Ninth Revision; ICD-10 = International Classification of Diseases, 10th Revision; NOAC = non-vitamin K antagonist oral anticoagulant; RECORD-AF = Registry on Cardiac Rhythm Disorders Assessing the Control of Atrial Fibrillation; TE = thromboembolism; TIA = transient ischemic attack

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were entered into the analysis. Among these, 1,237 patients with AF were identified, including 921 with newly diagnosed AF, thus providing 4,859 person-years of experience, and 316 who were re-hospitalized for AF (e-Fig 1). The Medical Ethics Committee of PLA General Hospital has been approved by the China Food and Drug Administration (registry number XZF20120145), and this ethics committee approved the present study (approval number 13BJZ40).

Evaluation of AF and Comorbidities

All individuals enrolled had a diagnosis of AF (*International Classification of Diseases, Ninth Revision* [ICD-9], or *International Classification of Diseases, 10th Revision* [ICD-10], codes 427.31 or I48). Information on comorbidities and events were also based on ICD-9 and ICD-10 codes. The index date was the first date of diagnosis of AF. Stroke and bleeding risks were assessed on the date of first diagnosis of AF.

AF was diagnosed based on an ECG or Holter recording. The inclusion criteria for an AF case was limited to inpatients with diagnosis of AF on admission and discharge. New-onset AF was defined as the individuals without AF at enrollment who subsequently developed AF after enrollment. To accurately verify the “true” patients with AF with a confirmed diagnosis, AF diagnosed at outpatient visits was excluded, as was atrial flutter. We excluded atrial flutter in this study because our focus was on the clinical epidemiology of AF specifically, and this would allow comparisons with other studies on the clinical epidemiology of AF in Western populations. For inpatients who had AF diagnosis on admission and discharge, the ECG could then be followed up to confirm the diagnosis of AF.

ICD-9 and ICD-10 codes for defined comorbidities are shown in e-Table 1. The definitions of various comorbidities are summarized in e-Table 2.

Stroke subtypes were classified into ischemic stroke (ICD-9 code 436, ICD-10 code I63) and hemorrhagic stroke (ICD-9 codes 430-432, ICD-10 codes I60.x, I61.x). Patients with major bleeding who required admission were identified. The major bleeding events were classed using ICD codes and medical data. Major bleeding was defined as an intracranial or extracranial hemorrhage or a decrease in the blood hemoglobin level of > 2.0 g/dL, the need for a transfusion of two or more units of blood, the need for surgery to achieve hemostasis, any combination of these events, or bleeding events needing in-hospital therapy.

Statistical Analysis

Continuous variables were tested for distribution by the Kolmogorov-Smirnov test. Those with a normal distribution were presented as a mean with SD and analyzed using the *t* test. Data with a non-normal distribution were presented as the median with interquartile range and were analyzed using the Mann-Whitney *U* test. The comparison of discrete variables was done via the χ^2 test.

Results

There were 1,237 patients with AF identified in the 11-year period, with 921 cases of newly diagnosed AF (4,859 person-years) entered into the final analysis after excluding 316 cases of rehospitalization for AF. The mean age was 70 years among 921 patients with AF patients (62% men).

Most patients ($n = 574$, 62.3%) were not taking any antithrombotic agents. Three hundred forty-seven (37.7%) were receiving antithrombotic treatment: 298 (32.3%), aspirin; 38 (4.1%), warfarin; and 11 (1.2%), clopidogrel (Table 1).

Antithrombotic drug use was calculated for stroke risk scores (CHADS₂ and CHA₂DS₂-VASC [congestive heart failure, hypertension, age ≥ 75 years (doubled), diabetes, stroke or transient ischemic attack (doubled), vascular disease, age 65 to 74 years, and female sex]) and bleeding risk score (HAS-BLED [hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly (> 65 years), drugs/alcohol concomitantly]) for female and male subjects over time separately, and for different age categories (age 20-64 years, age 65-74 years, and age ≥ 75 years). Given that patients with AF in this cohort started receiving antithrombotic drugs in 2007, the average annual rate of change (or increase) in antithrombotic drug use for women and men was calculated by taking the mean difference in antithrombotic drug-use rates between consecutive years. *P* values for trend in anticoagulant use over time for women and men was calculated with the Jonckheere trend test.

The annual stroke and bleeding rates were calculated as the events by total number of patients with AF and by total person-years between 2001 and 2012, respectively. The annual stroke and bleeding rate estimates were also calculated for those not taking anticoagulant medication, and those taking aspirin and warfarin, between 2001 and 2012.

Multivariate analysis was used to assess anticoagulant use (ie, warfarin, aspirin) or no anticoagulant and the occurrence of stroke and major bleeding, respectively. Hazard ratios (HRs) of anticoagulant use for stroke were estimated by a Cox proportional hazard model that included anticoagulant drug as a time-dependent covariate and adjusted for baseline variables.

A sensitivity analysis of time trends of antithrombotic therapy with relation to stroke and bleeding events excluded patients with rheumatic heart disease and hyperthyroidism. To compare the time trends in anticoagulant use relative to stroke rates among Western and Chinese populations with AF, the various studies on AF were selected by region; that is, Europe, North America (specifically, the United States and Canada), international regions (including Asia), and China. The selected studies were those with large sample sizes ($> 1,000$ people), including data from Medicare claims, health insurance, veterans' health records, and prospectively observational registries (ie, the National Cardiovascular Data Registry). Clinical trial cohorts were excluded, as they were unlikely to reflect real-world community populations, owing to restrictive trial eligibility criteria. The included studies are shown in e-Table 3). The overall trend line was drawn to roughly observe the changes in anticoagulant use over time among the different AF populations, compared with China.

A *P* value $< .05$ was considered statistically significant. The 95% CIs were calculated based on Poisson distribution. Statistical analysis was performed using IBM SPSS Statistics, version 21.0 (IBM).

Antithrombotic Treatment Related to Stroke or Bleeding Risk Scores

There were no significant differences in the CHADS₂, CHA₂DS₂-VASC, and HAS-BLED scores between patients without antithrombotic treatment and patients with antithrombotic treatment (Table 1). When patients were classified by CHADS₂ and CHA₂DS₂-VASC scores, the use of antithrombotic treatment did not increase with higher stroke risk scores (CHADS₂ score, $P = .522$; CHA₂DS₂-VASC score, $P = .957$) (e-Fig 2). When bleeding risk was stratified by HAS-BLED score, the use of

TABLE 1 Baseline Characteristics of 921 Patients With AF

Characteristics	Patients With AF Not Receiving ATT (n = 574)	Patients With AF Receiving ATT (n = 347)	P Value
Age, mean (SD), y	70 (11)	69 (11)	.116
Male sex	356 (62.0)	218 (62.8)	.807
Medical history			
Hypertension	132 (23.0)	104 (30.0)	.019 ^a
Coronary artery disease	121 (21.1)	66 (19.0)	.451
Heart failure	33 (5.7)	10 (2.9)	.046 ^a
Diabetes	13 (2.3)	16 (4.6)	.048 ^a
COPD	16 (2.8)	9 (2.6)	.861
Rheumatic heart disease	16 (2.8)	5 (1.4)	.185
Hyperlipidemia	8 (1.4)	10 (2.9)	.114
Dilated cardiomyopathy	5 (0.9)	6 (1.7)	.245
Peripheral vascular disease	6 (1.0)	3 (0.9)	.787
Renal dysfunction	6 (1.0)	2 (0.6)	.457
Hyperthyroidism	4 (0.7)	1 (0.3)	.413
Prior stroke	24 (4.2)	22 (6.3)	.145
CHADS ₂ score, median (IQR)	1 (0-1)	1 (0-1)	.429
CHA ₂ DS ₂ -VASc score, median (IQR)	2 (1-3)	2 (1-3)	.884
HAS-BLED score, median (IQR)	1 (1-1)	1 (1-2)	.224
Drugs			
β-Blocker	89 (15.5)	233 (67.1)	< .001 ^a
Diuretic	116 (20.2)	153 (44.1)	< .001 ^a
ACE/ARB	65 (11.3)	132 (38.0)	< .001 ^a
Antacid drug ^b	75 (13.1)	119 (34.3)	< .001 ^a
CCB	70 (12.2)	107 (30.8)	< .001 ^a
Digoxin	60 (10.5)	87 (25.1)	< .001 ^a
Statin	23 (4.0)	121 (34.9)	< .001 ^a
Nitrate	28 (4.9)	54 (15.6)	< .001 ^a

Data given as No. (%) unless otherwise indicated. ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ARB = angiotensin receptor blocker; ATT = antithrombotic treatment; CCB = calcium antagonist; CHADS₂ = congestive heart failure, hypertension, age ≥ 75 y, diabetes, stroke (doubled); CHA₂DS₂-VASc = congestive heart failure, hypertension, age ≥ 75 y (doubled), diabetes, stroke or transient ischemic attack (doubled), vascular disease, age 65-74 years, and female sex; HAS-BLED = hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly (> 65 y), and concomitant drug (eg, aspirin, nonsteroidal antiinflammatory drugs) and alcohol use; IQR = interquartile range.

^aStatistically significant at $P < .05$.

^bAntacid drugs include H₂-receptor antagonists and proton pump inhibitors.

antithrombotic treatment was 23.0% in low-risk patients (0-1) and 28.0% in patients at intermediate (2) or high risk (≥ 3) ($P = .095$) (e-Fig 2).

Time Trends of Antithrombotic Treatment Related to Sex and Age

The use of antithrombotic treatment (mainly aspirin) increased in women and men over time, especially during the last 6 years. The rate of aspirin treatment increased from 4.0% in 2007 to 46.1% in 2012 in women, and from 7.7% in 2007 to 61.9% in 2012 in men. The rate of warfarin treatment rose from 4.4% in 2009 to 7.7% in 2012 in

women, and from 4.3% in 2009 to 9.5% in 2012 in men (P value for trend for both, $P < .005$) (Fig 1). There was no significant difference in type of antithrombotic treatment between age groups (age 20-64 years, 65-74 years, and > 75 years, $P = .361$) (e-Fig 3).

Time Trends of Antithrombotic Treatment Related to Stroke and Bleeding Events

There were 59 ischemic strokes (6.4%) and 13 major bleeding events (1.4%), including seven hemorrhagic strokes, five GI hemorrhage, and one respiratory-related hemorrhage.

Figure 1 – Time trends in antithrombotic treatment related to sex. ATT = antithrombotic treatment.

The rate of ischemic stroke was 6% in patients without antithrombotic treatment, 7% in patients taking aspirin, and 13% in patients taking warfarin over the studied decade. This translated to 0.01 person-years both in patients without antithrombotic treatment and those taking aspirin, and 0.02 person-years in patients taking warfarin (Table 2). Bleeding rates were 2% in patients without antithrombotic treatment over an 11-year period, 1% in those taking aspirin since 2007, and 3% in those on warfarin since 2009, which translates to 0.34 per 100 person-years without antithrombotic treatment, 0.16 per 100 person-years on aspirin, and 0.47 per 100 person-years on warfarin (Table 3).

In the whole cohort, the annual stroke rate was approximately 6%, and annual rate of bleeding events was about 1% (e-Table 4). Time trends of stroke and bleeding events related to antithrombotic treatment are shown in Figure 2. Occurrences of both stroke and bleeding events increased over time, with bleeding rates increasing with the higher use of antithrombotic treatment.

HR for the Risk of Stroke and Bleeding Events Associated With Antithrombotic Treatment

Using a Cox proportional hazard model, the HR (95% CI) for ischemic stroke in subjects not receiving antithrombotic treatment was 0.68 (0.39-1.18) compared with those taking aspirin and 1.39 (0.54-3.59) compared with those taking warfarin (e-Fig 4). A sensitivity analysis of time trends of antithrombotic therapy relative to stroke and bleeding events showed similar results, excluding people with rheumatic heart disease and hyperthyroidism (data not shown).

Comparisons With Europe and North America

A comparison of time trends in anticoagulant use related to stroke among Europe, North America, and China is shown in Figure 3. In more recent studies, use of oral anticoagulant drugs increased by approximately 20% in both Europe (eg, from 61% in Europe Heart Survey⁹ to 80% in the EuroObservational Research Program Atrial Fibrillation³) and North America (eg, from 30% in a Minnesota community-based study⁴ to 55% in the PINNACLE Registry²). In China, this increase is about 7%, based on hospital studies (eg, from 7% in a study by the Chinese Society of Cardiology¹⁰ to 14% in a study by Guo et al¹¹), with warfarin use ranging from 3% to 14% in mainland China.¹²⁻¹⁴ Oral anticoagulant use is much lower in China compared with North America and Europe, while stroke rates in the Chinese population with AF are much higher than in the population with AF in Western countries (Fig 3).

Discussion

In this study, we show, first, that the use of antithrombotic treatment, mainly aspirin, has increased over the last decade in Chinese patients with newly diagnosed AF, but the annual stroke rate remains at about 6%. Second, the prescription of antithrombotic drugs had little relationship to stroke or bleeding risk scores, but anticoagulation rates were far lower than in patient populations with AF in Europe and North America. Third, bleeding risk increased with the increased use of antithrombotic treatment (eg, aspirin and warfarin) in this Chinese population. Fourth, neither aspirin nor warfarin adequately reduced stroke risk in this real-world population of Chinese patients with AF over the last decade, reflecting the inefficacy of aspirin and (likely) poor anticoagulation control among warfarin users.

TABLE 2] Strokes Related to ATT in Patients With AF

Year	No ATT (n = 574)						Aspirin (n = 298)						Warfarin (n = 38)					
	Stroke	Total Patients, No.	Stroke Rate, %	Person-y, No.	Stroke Rate, Person-y	95% CI	Stroke	Total Patients, No.	Stroke Rate, %	Person-y, No.	Stroke Rate, Person-y	95% CI	Stroke	Total Patients, No.	Stroke Rate, %	Person-y, No.	Stroke Rate, Person-y	95% CI
2001	0	1	0.00	0	0.00	0.00-0.00	...	...	...	...	...	...	...	...	...	...	...	...
2002	0	11	0.00	4	0.00	0.00-0.00	...	...	...	...	...	...	...	...	...	...	...	...
2003	0	12	0.00	7	0.00	0.00-0.00	...	...	...	...	...	...	...	...	...	...	...	...
2004	0	14	0.00	8	0.00	0.00-0.00	...	...	...	...	...	...	...	...	...	...	...	...
2005	1	23	0.04	32	0.03	0.01-0.15	...	...	...	...	...	...	...	...	...	...	...	...
2006	1	35	0.03	126	0.01	0.00-0.04	...	...	...	...	...	...	...	...	...	...	...	...
2007	3	29	0.10	113	0.03	0.01-0.07	0	2	0.00	9	0.00	0.00-0.00	...	...	...	...	...	...
2008	6	73	0.08	369	0.02	0.01-0.03	0	2	0.00	14	0.00	0.00-0.00	...	...	...	...	...	...
2009	6	63	0.10	314	0.02	0.01-0.04	2	22	0.09	140	0.01	0.00-0.05	0	1	0.00	8	0.00	0.00-0.00
2010	8	105	0.08	594	0.01	0.01-0.03	4	57	0.07	362	0.01	0.00-0.03	0	3	0.00	8	0.00	0.00-0.00
2011	3	93	0.03	507	0.01	0.00-0.02	7	89	0.08	562	0.01	0.00-0.02	2	13	0.15	63	0.03	0.01-0.10
2012	5	115	0.04	576	0.01	0.00-0.02	8	126	0.06	845	0.01	0.00-0.02	3	21	0.14	133	0.02	0.01-0.06
Total	33	574	0.06	2650	0.01	0.00-0.02	21	298	0.07	1932	0.01	0.00-0.02	5	38	0.13	212	0.02	0.01-0.05

See Table 1 legend for expansion of abbreviations.

TABLE 3] Bleeding Events Related to ATT in Patients With AF

Year	No ATT (n = 574)						Aspirin (n = 298)						Warfarin (n = 38)					
	Bleeding Events	Total Patients, No.	Rate of Bleeding Events, %	Person-y, No.	Rate of Bleeding Events per 100 Person-y	95% CI	Bleeding Events	Total Patients, No.	Rate of Bleeding Events, %	Person-y, No.	Bleeds Rate, per 100 Person-y	95% CI	Bleeding Events	Total Patients, No.	Rate of Bleeding Events, %	Person-y, No.	Rate of Bleeding Events per 100 Person-y	95% CI
2001	0	1	0.00	0	0.00	0.00-0.00	...	...	...	...	...	...	...	...	...	...	...	...
2002	0	11	0.00	4	0.00	0.00-0.00	...	...	...	...	...	...	...	...	...	...	...	...
2003	0	12	0.00	7	0.00	0.00-0.00	...	...	...	...	...	...	...	...	...	...	...	...
2004	0	15	0.00	10	0.00	0.00-0.00	...	...	...	...	...	...	...	...	...	...	...	...
2005	0	23	0.00	32	0.00	0.00-0.00	...	...	...	...	...	...	...	...	...	...	...	...
2006	0	36	0.00	130	0.00	0.00-0.00	...	...	...	...	...	...	...	...	...	...	...	...
2007	0	29	0.00	113	0.00	0.00-0.00	0	2	0	9	0.00	0.00-0.00	...	...	...	...	...	...
2008	2	74	0.03	376	0.53	0.48-0.58	0	2	0	14	0.00	0.00-0.00	...	...	...	...	...	...
2009	1	63	0.02	314	0.32	0.26-0.37	0	22	0	140	0.00	0.00-0.00	0	1	0.00	8	0.00	0.00-0.00
2010	1	102	0.01	581	0.17	0.14-0.20	0	57	0	362	0.00	0.00-0.00	0	3	0.00	8	0.00	0.00-0.00
2011	2	93	0.02	507	0.39	0.35-0.43	0	89	0	563	0.00	0.00-0.00	0	13	0.00	63	0.00	0.00-0.00
2012	3	115	0.03	576	0.52	0.48-0.56	3	126	0.02	844	0.36	0.32-0.38	1	21	0.05	133	0.75	0.67-0.81
Total	9	574	0.02	2,650	0.34	0.32-0.36	3	298	0.01	1932	0.16	0.14-0.17	1	38	0.03	212	0.47	0.40-0.54

See Table 1 legend for expansion of abbreviations.

Figure 2 – Time trends of ATT related to stroke and bleeding events in 921 patients with AF. AF = atrial fibrillation. See Figure 1 legend for expansion of other abbreviation.

In the early 2000s, reported warfarin use was only 0.5% to 9.1% in China, being 0.5% to 2.7% in community-based data and 6.6% to 9.1% according to hospital-based data.^{10,12-14} The prevalence of stroke or TE was as high as 13.4% to 24.2% during the same time.^{10,12-14} In the present community study, use of antithrombotic drugs (including warfarin) mainly increased in the late 2000s, but with an overall warfarin use of only 4% and the annual stroke rate still being 6%. Warfarin use was much higher in the hospital-based data compared with community-based data,¹⁵ but the underuse of warfarin was still common in China, as is seen in many Asian countries.⁵ On the other hand, aspirin is still overused in

Chinese patients with AF, especially in the elderly population. In our previous hospital-based AF cohort, 60% of patients were on aspirin and only 14% patients were on warfarin. This was confirmed in a recent report of 9,727 Chinese patients with AF, which showed that 40% were taking aspirin compared with 20% taking warfarin.¹⁶ The high rate of aspirin use could reflect the fear of bleeding with warfarin, which is the main oral anticoagulant available in China.

To date, three international observational studies on AF have enrolled patients from Asian countries.¹⁷⁻²¹ In these studies, about one-half of the patients with AF

Figure 3 – Time trends in anticoagulant use and stroke rate in populations of patients with AF in Europe, North America, China, and in international studies. AFFECTS = Atrial Fibrillation Focus on Effective Clinical Treatment Strategies; EORP-AF = EuroObservational Research Program Atrial Fibrillation; GARFIELD = The Global Anticoagulant Registry in the Field; OAC = oral anticoagulant; PREFER in AF = Prevention of Thromboembolic Events, European Registry in Atrial Fibrillation; REACH = The Reduction of Atherothrombosis for Continued Health; RECORD AF = Registry on Cardiac Rhythm Disorders Assessing the Control of Atrial Fibrillation; RECORD AF-Asia Pacific = Registry on Cardiac Rhythm Disorders Assessing the Control of Atrial Fibrillation, Asia Pacific; TREAT-AF = The Retrospective Evaluation and Assessment of Therapies in AF study. See Figure 2 legend for expansion of other abbreviation.

were given warfarin and the rates of warfarin use were much lower in the Asian subgroup with AF.^{17,18} Aspirin was still the common antithrombotic drug used. In the Registry on Cardiac Rhythm Disorders Assessing the Control of Atrial Fibrillation (RECORD-AF), in which 52% of patients were taking warfarin and 42%, aspirin, the Asian subgroup (RECORD-AF-Asia Pacific study) involved 2,721 patients (36% Chinese) and reported that 36% were on warfarin and 51% were on aspirin from 2007 to 2008.¹⁸ The difference in warfarin use in the RECORD-AF-Asia Pacific study and in this study could perhaps be related to prescribing habits (a province in China vs other Asia-Pacific countries with advanced health-care systems) or the data source, especially since RECORD-AF is an industry-funded commercial study and the present study is based on an administrative dataset. The rate of warfarin use in RECORD-AF-Asia Pacific probably represents the level of warfarin use in other Asian countries apart from China (ie, only 951 Chinese among the 2,629 Asian patients).¹⁸ Similarly, the Reduction of Atherothrombosis for Continued Health (REACH) Registry recruited 16% Asian and 0.1% Chinese patients.¹⁹ Among 4,582 patients with AF (90% of patients with CHADS₂ score ≥ 1), the rate of warfarin use was 52% (including 16% taking warfarin plus an antiplatelet medication) and aspirin was used in 50%, with a 7.7% stroke rate over a 4-year follow-up.²⁰ In the first cohort of 10,614 patients from 2009 to 2011, the Global Anticoagulant Registry in the Field (GARFIELD), included 24% Asians (0.7% Chinese) with newly diagnosed AF.²¹ Most of those patients were at moderate to high risk for TE (92% patients with CHADS₂ score ≥ 1 , 97% patients with CHA₂DS₂-VASc score ≥ 1), of whom 58% patients were on warfarin, and 14% of these patients had prior stroke or TIA.²²

The relatively high rate of warfarin use in these international studies was more likely to be driven by the increased use (ie, $> 20\%$ in recent decades) of anticoagulant drugs in Europe and North America. Over recent decades, warfarin use has ranged from 40% to 83% in European countries, while the annual stroke rate was 1% to 5%²²⁻²⁶ (e-Fig 5). Indeed, three AF surveys across European countries (Euro Heart Survey, EuroObservational Research Program Atrial Fibrillation, and the Prevention of Thromboembolic Events-European Registry in Atrial Fibrillation survey) confirmed a high overall rate of anticoagulant use in European clinical practice,^{3,9,27} achieving about 80% (6% to 8% patients on NOACs) more recently. Even so, prior stroke or TIA or

thromboembolic event among these patients with AF remained at 10% to 15%.

Broadly, oral anticoagulant use was slightly lower in North America compared with Europe.^{2,28-30} Nonetheless, compared with the Minnesota community-based study (1995-2000; warfarin used by 30% of patients), warfarin use increased by about 25% in the National Cardiovascular Data Registry PINNACLE Program (2008-2009; warfarin use by 50% of patients).⁴ Stroke rates in AF currently range from 0.5% to 2.0% in America.^{2,27-29} However, the prevalence of stroke or TIA was still 7.7%, and was 1.3% for hemorrhagic stroke at primary cardiovascular hospitalization of patients newly diagnosed with AF.³¹ Similar anticoagulant use (32% in 1995; 60% in 2007) and stroke rate (1.7% in 1995; 2.1% in 2007) was seen in Canada.^{32,33}

Antithrombotic therapy use (essentially warfarin and aspirin) increased in the late 2000s in China, with large variations across practice. However, aspirin (usually 100 mg) remains the common antithrombotic drug choice, and warfarin was widely underused in real-world practice in China. This low rate of warfarin use in Chinese patients with AF is similar to that seen in North America 20 years ago, and was far lower than that seen in European patients with AF. Moreover, the use of aspirin or warfarin did not reduce stroke risk in this real-world Chinese population with AF, while the bleeding risk did seemly increase, consistent with the findings of our previous hospital-based study on AF.¹⁵ The lack of aspirin efficacy is unsurprising, but the poor efficacy of warfarin in reducing stroke rates overall may reflect poor quality of anticoagulation control, given the need for regular anticoagulation monitoring to achieve a time in therapeutic range $> 70\%$, which is hardly achieved in China.

Limitations

There are several limitations inherent to this observational study. First, health insurance data would likely result in an underestimate of AF if medical records were incomplete. The incidence of AF, together with that of stroke or major bleeding, also could have been underestimated without opportunistic screening for AF in this medical insurance database. We also identified patients with AF based on “objective” evidence (eg, ECG, 24-h Holter), which at least could be confirmed in the inpatients’ medical records. Indeed, we have not studied outpatients; we are less confident in the nonhospital diagnosis of AF for this group, as it may not be ECG verified, and AF diagnosis could possibly have been made clinically.

Second, there were 21 patients with rheumatic heart disease in this dataset, given it was a real-world investigation in China. While this could have an impact on the outcome, a sensitivity analysis excluding patients with rheumatic heart disease showed similar results. For the limited number of patients on oral anticoagulant therapy and small number of major bleeding events, we did not perform a Cox hazard model analysis to compare HRs of warfarin, aspirin, and nonanticoagulation on bleeding risk in this cohort. Also, the efficacy comparisons of warfarin, aspirin, and nonanticoagulation are limited by the nonrandomized comparisons, modest numbers, residual confounding from comorbidities, and lack of data on anticoagulation control (eg, time in therapeutic range values).³³⁻³⁶ Finally, NOACs (initially dabigatran, followed by others) only became available in 2013 in China, and the present analysis does not address the impact of NOACs for stroke prevention in China.

Conclusions

Antithrombotic use, mainly aspirin, increased among Chinese patients newly diagnosed with AF, with no relationship to assessment of the patients' stroke/bleeding risk. Oral anticoagulation use was very low. Given the health-care burden of AF and its complications, our study has major implications for health-care systems in non-Western countries, given the global burden of this common arrhythmia.

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