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Neurology care and the long-term outcomes of atrial fibrillation-related ischaemic stroke in China: median 3-year outcome from a high volume academic tertiary hospital

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ABSTRACT

Objectives The initial medical contact of patients with atrial fibrillation (AF) and ischaemic stroke is often performed by neurologists. However, when stand care with oral anticoagulants (OACs) adherence and persistence was emphasised by cardiologists, data regarding the gap between current neurology care and standard care from Chinese tertiary hospitals is scarce and the long-term outcome is unknown. This study was to investigate the AF detection rate, the use of anticoagulation therapy and posthospital clinical outcomes associated with neurology care in patients with AF and ischaemic stroke in China.

Design A retrospective cohort study.

Setting Clinical data of all patients who had an ischaemic stroke discharged from the neurologic department of a high-volume academic hospital from 1 January 2013 to 31 December 2017 were analysed and patients were followed.

Participants Patients diagnosed with ischaemic stroke and AF were included.

Main outcome measures The usage of anticoagulation at discharge, the posthospital restroke rate and all-cause mortality.

Results Among 5797 patients who had an ischaemic stroke, 373 (6.43%) patients were diagnosed with AF during hospitalisation. Among them, only 198 (53.66%) patients were on anticoagulation therapy at discharge. A total of 325 (88.08%) patients were accessible and received follow-up. After a median 3-year follow-up, 103 (31.69%) patients died due to all causes. Among them, 53 (16.31%) patients died from recurrent stroke. And 86 (26.46%) patients restroked. In multivariable analysis, patients without anticoagulation therapy, muscle strength<grade 3 at discharge, coronary artery disease and advanced age predicted the recurrent stroke.

Conclusions Secondary stroke prevention in AF patients associated with neurology care is challenging in China, as manifested by a lower AF detection rate, significant underuse of OACs, high mortality and recurrent stroke rate. Efforts to increasing the AF detection rate and reinforce education on neurologists should be made to improve neurology care and intensify posthospital management in such patients.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Clinical data of all patients who had an ischaemic stroke discharged from the neurologic department were analysed.
⇒ To investigate the long-term outcome, a median 3-year follow-up was conducted in patients with ischaemic stroke and atrial fibrillation (AF).
⇒ This study was performed at a large tertiary hospital in China and the results might not represent real-world neurology care for secondary stroke prevention in all AF patients.

INTRODUCTION

The incidence of recurrent stroke in patients with atrial fibrillation (AF) who have experienced a previous stroke is approximately 5.8%–21.5% over a period of 1.65–5 years,[1 2] and the long-term results are unexpectedly worse, especially in those patients who are unwilling to adhere to oral anticoagulants (OACs).[1–7] Although there is clear evidence that OACs can mitigate the risk of stroke by two-thirds,[8] challenges and concerns of secondary stroke prevention with OACs persist. The biggest hurdle in neurology care is that, both patients and neurologists care more about bleeding events in the acute phase of stroke. The reported prescription rate of OACs in AF patients diagnosed with ischaemic stroke by neurologists was approximately 20% in China, and the persistence of OACs was very poor,[9 10] even in the era of novel oral anticoagulants (NOACs). However, the long-term clinical outcomes of this undertreatment have scarcely been reported. The recurrence of stroke is not only associated with higher disability and mortality, but also leading to a great burden on both the family and the national healthcare system. This

study was to investigate the AF detection rate, the use of anticoagulation therapy and long-term outcomes associated with neurology care in patients with AF and ischaemic stroke in China.

METHODS

Study design and population

This single-centre retrospective investigation was performed in a large tertiary hospital in China. The tertiary hospital is the first affiliated hospital to a medical university located at eastern China, staffed by around 7000 employees, with a bed capacity of 5200 and the average annual admissions of 180 000 around. From 1 January 2013 to 31 December 2017, all patients discharged from the department of neurology were screened. Eligibility requirements included: (1) aged 18–85 years; (2) diagnosed with ischaemic stroke or transient ischaemic attack (TIA) by CT or MRI and assessed by neurologists; and (3) diagnosed with a history of AF, either detected previously or during hospitalisation. The exclusion criteria were as follows: (1) haemorrhagic stroke; (2) aged<18 years; and (3) valvular heart disease or patent fossa ovalis.

During hospitalisation at the neurology department, stroke care including cerebral image assessments, transthoracic echocardiogram, ECG, ultrasound examination of the cervical arteries, routine lipid profile, liver enzymes and creatinine was routinely performed. In non-valvular AF (NVAF) population, diagnosis of AF was established based on a 12-lead ECG or 24-hour Holter monitoring either before or during hospitalisation. Secondary stroke prevention and the control of other cardiovascular comorbidities were initiated by the neurologists. All the basic characteristics and hospital managements were collected from the medical records retrospectively. At a median 3 years after discharge, all patients were followed up once with clinic visits or telephone interviews which were performed by research personnel. Clinical data from medical records, including patient demographics, healthcare insurance status, cardiovascular risk factors, medications, laboratory tests and follow-up results, were extracted by trained research coordinators.

Patient and public involvement

None.

Statistical analysis

Continuous variables were reported as means and SD if normally distributed or medians (IQR) if not. Categorical variables are expressed as numbers and percentages. Univariable and multivariable logistic regression analyses were performed to determine independent predictors for recurrent stroke and all-cause death. All statistical analyses were performed using SPSS Statistics (V.21). Statistical significance was set at a two-sided p<0.05.

Table 1 Baseline characteristics

Characteristics	
Age, years (x±s)	73.21±10.12
<65	70 (18.77%)
≥65 and <75	112 (30.03%)
≥75	191 (51.21%)
Male, n (%)	201 (53.89%)
Atrial fibrillation history, n (%)	178 (47.72%)
Comorbidities	
Coronary artery disease, n (%)	99 (26.54%)
Hypertension, n (%)	269 (72.12%)
Diabetes, n (%)	97 (26.01%)
EHRA 2 valvular disease*, n (%)	38 (10.19%)
Cardiomyopathy†, n (%)	5 (1.34%)
CHA_2DS_2-VASc Score, (x±s)	4.97±1.44
2	18 (4.83%)
3	49 (13.14%)
4	69 (18.50%)
5	88 (23.59%)
6	95 (25.47%)
7	48 (12.87%)
8	6 (1.61%)
Anticoagulation therapy before admission	43 (11.53%)
Warfarin	38 (88.37%)
NOACs	5 (11.63%)

*Patients without mitral stenosis (moderate–severe of rheumatic origin) or mechanical prosthetic valve replacement, including mitral regurgitation, mitral valve repair, aortic stenosis, aortic regurgitation, tricuspid regurgitation, tricuspid stenosis and bioprosthetic valve replacements.
†Patients with hypertrophic cardiomyopathy or dilated cardiomyopathy.
EHRA, European Heart Rhythm Association valvular heart disease classification; NOACs, novel oral anticoagulants.

RESULTS

AF prevalence in this entire ischaemic stroke cohort

During the study period, 5797 patients were diagnosed with ischaemic stroke or TIA. In these patients, 373 patients were found to have AF and the AF detection rate was 6.43%.

The baseline characteristics of the 373 stroke patients with AF are shown in table 1. The average age of these patients was 73.21±10.12 years, with more than half being≥75 years. Overall, 53.89% of these patients were men. The average CHA_2DS_2-VASc Score was 4.97±1.44. Among them, 178 had known AF before admission, while the remaining 195 patients were first diagnosed with AF accounting for 3.36% of the population who had a stroke.

In-hospital management and poststroke anticoagulation rate at discharge

Among 373 patients with AF, 286 (76.68%) were admitted for a new onset of stroke, while the remaining

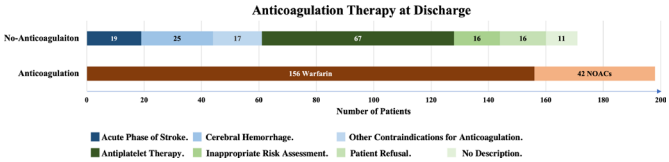

Figure 1 Anticoagulation therapy at discharge. Anticoagulants were prescribed for 198 (53.66%) patients at discharge. NOACs, novel oral anticoagulants.

87 (23.32%) were admitted for neurological sequelae of stroke. Overall, 4 patients (1.07%) died of stroke in hospital, and 99 patients were discharged with at least 1 side of limb muscle strength less than grade 3. In these patients with AF, anticoagulants were prescribed for only 198 (53.66%) patients (156 on warfarin and 42 on NOACs) for secondary stroke prevention at discharge, and 110 (29.81%) patients without any contraindications of anticoagulants were not treated with OACs (figure 1). Cardiologist consultation for these stroke patients with AF was only invited in 94 (25.2%) patients.

Follow-up rate, death rate and restroke rate of secondary stroke prevention in the NVAF population

After a median follow-up of 3 years, a total of 325 (88.08%) patients were adherent to the follow-up programme. Among them, 86 (26.46%) patients had a recurrent stroke. In these patients, 53 patients died directly of recurrent stroke or indirectly due to its related events, accounting for a recurrent stroke mortality rate as high as 16.31%. The average age of these patients with recurrent stroke-related deaths was 78.68±8.99 years, and the average CHA_2DS_2-VASc Score was 5.55±1.35, both of which were higher than that of the overall population (78.68±8.99 vs 73.21±10.12, p<0.001; 5.55±1.35 vs 4.97±1.44, p=0.006). Non-stroke-related deaths occurred in 50 patients, with an all-cause death rate of 31.69%.

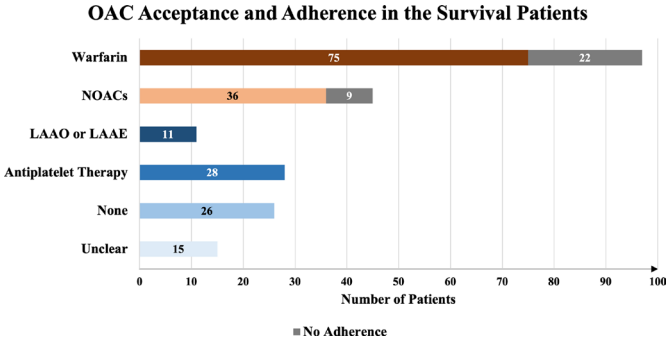

Figure 2 OAC acceptance and adherence in the survival patients. Among 222 survival patients, 45 (20.27%) received NOACs and 97 (43.69%) received warfarin. Only 36 (80.00%) patients with NOACs and 75 (77.32%) with warfarin continued OAC therapy over the whole follow-up period. LAAE, thoracoscopic left atrial appendage excision; LAAO, percutaneous left atrial appendage occlusion; NOACs, novel oral anticoagulants; OAC, oral anticoagulant.

OAC acceptance and adherence in the survival patients

Among 222 survival patients (figure 2), 11 (4.95%) underwent percutaneous left atrial appendage occlusion or thoracoscopic left atrial appendage excision, 45 (20.27%) received NOACs and 97 (43.69%) received warfarin at discharge. At the time of clinic visits or telephone interviews conducted, only 36 patients with NOACs and 75 with warfarin continued OAC therapy without any interruption over the whole follow-up period, with adherence rates of 80.00% and 77.32%, respectively.

Risk factors for recurrent stroke and all-cause deaths

In the univariable logistic regression, age, coronary artery disease, hypertension, CHA_2DS_2-VASc Score, muscle strength less than grade 3 and no anticoagulation therapy at discharge were significantly related to stroke recurrence (table 2). After adjustment in the multivariable logistic regression, advanced age (OR=1.06; 95% CI=1.03 to 1.10; p<0.01), coronary artery disease (OR=1.84; 95% CI=1.05 to 3.22; p=0.03), muscle strength less than grade 3 (OR=1.85; 95% CI=1.04 to 3.26; p=0.04) and no anticoagulation therapy at discharge (OR=0.53; 95% CI=0.31 to 0.90; p=0.02) remained statistically significant. Moreover, in the multivariable logistic regression analysis of all-cause deaths, age (OR=1.09; 95% CI=1.06 to 1.13; p<0.01) and muscle strength less than grade 3 at discharge (OR=2.91; 95% CI=1.67 to 5.06; p<0.01) were significantly correlated with all-cause deaths (table 3).

DISCUSSION

OAC therapy for the secondary prevention of thromboembolic events is the biggest dilemma for neurologists since the majority of the population has both high CHA_2DS_2-VASc scores (clinical estimation of the risk of stroke including congestive heart failure, hypertension, age >75 years, diabetes mellitus, prior stroke, vascular disease, age 65~75 years, female sex) and HAS-BLED scores (clinical estimation of the risk of hemorrhage including hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, age >65 years, drugs/alcohol concomitantly).[4 5 9 11] In this situation, OAC is 'a knife with two blades'. On one hand, the prescription of OACs for secondary stroke prevention in AF patients can significantly reduce thromboembolic events; on the other hand, it can also increase bleeding events, especially intracranial haemorrhage. As such, OAC therapy by neurologists was less prescribed, and the patients themselves were less likely to accept OACs for secondary prevention.[9] Limitations of warfarin and the high cost of NOACs further worsened this predicament in China according to previous reports.[12 13] However, the long-term prognosis of this lukewarm attitude toward OAC therapy in this unique population remains unknown. In our retrospective observational study, we surprisingly found: (1) a lower AF detection rate; (2) a lower OAC prescription rate and poor long-term compliance; (3) a higher follow-up loss rate; and (4) a higher restroke rate and higher mortality. From these findings, we suggest the

Table 2 Risk factors of recurrent stroke

	Univariable regression		Multivariable regression	
	OR (95% CI)	P value	OR (95% CI)	P value
Age	1.07 (1.04 to 1.11)	<0.01	1.06 (1.03 to 1.10)	<0.01*
Male	1.26 (0.77 to 2.07)	0.36		
Coronary artery disease	2.24 (1.31 to 3.81)	<0.01	1.84 (1.05 to 3.22)	0.03*
Hypertension	1.86 (1.02 to 3.37)	0.04		
Diabetes	1.65 (0.96 to 2.85)	0.07		
CHA_2DS_2-VASc Score	1.54 (1.27 to 1.86)	<0.01		
Cardiology consultation in hospital	0.87 (0.49 to 1.54)	0.62		
Muscle strength < grade 3 at discharge	1.93 (1.13 to 3.30)	0.02	1.85 (1.04 to 3.26)	0.04*
Anticoagulation therapy at discharge	0.46 (0.28 to 0.76)	<0.01	0.53 (0.31 to 0.90)	0.02*

* $p<0.05$, statistical significance in the multivariable regression.

following measures to improve the long-term prognosis to both neurologists and healthcare decision-makers:

1. Improve AF screening facilities to increase the AF detection rate in this population.

In patients presenting with ischaemic stroke or TIA, nearly a quarter have underlying AF, as a recent study reported the AF detection rate was as high as 28% by using additional prolonged Holter monitoring.[14] However, AF is often paroxysmal and can evade detection. Previous studies have demonstrated inconsistent AF detection rate in terms of the AF screening facilities and screening protocol, for example, the AF detection rate was reported as low as 5.4%–7.7% using a 24-hour Holter electrocardiography or continuous stroke unit ECG monitoring.[15] Long-term monitoring devices, including implantable cardiac monitors, are superior to conventional follow-up for detecting AF after cryptogenic stroke; however, their use may be limited by costs and concerns for adverse events of the implantation procedure.[16] In our study, the AF detection rate in patients who had an ischaemic stroke was only 6.43% (including the newly detected AF), indicating that the usage of long-term monitoring devices was limited and the efforts of AF screening after ischaemic stroke by neurologists was insufficient.

Although there are numerous devices for detecting AF after stroke, the lack of an effective AF screening protocol post stroke is still a challenging problem in the neurologic department. With the development of newly applied prolonged non-invasive monitoring systems, such as AF-sensing watches,[17] wearable ECG telemonitoring systems and mobile one-lead ECG devices,[18 19] the situation will likely be improved.

2. Enhance education for both physicians and patients to improve the OAC prescription rate and to increase patient adherence.

Since stroke care is often initiated by neurologists, most AF-related patients who had a stroke are admitted to the neurology department. However, the management of AF-related strokes is quite different from that of other patients who had a stroke. OACs are certainly the leading

Table 3 Risk factors of all-cause deaths

	Univariable regression		Multivariable regression	
	OR (95% CI)	P value	OR (95% CI)	P value
Age	1.09 (1.06 to 1.13)	<0.01	1.09 (1.06 to 1.13)	<0.01*
Male	1.06 (0.66 to 1.70)	0.8		
Coronary artery disease	1.65 (0.99 to 2.77)	0.06		
Hypertension	1.01 (0.60 to 1.70)	0.97		
Diabetes	0.93 (0.54 to 1.60)	0.79		
CHA_2DS_2-VASc Score	1.36 (1.14 to 1.61)	<0.01		
Cardiology consultation in hospital	1.25 (0.74 to 2.12)	0.41		
Muscle strength<grade 3 at discharge	2.87 (1.71 to 4.80)	<0.01	2.91 (1.67 to 5.06)	<0.01*
Anticoagulation therapy at discharge	0.82 (0.51 to 1.31)	0.41		

** $p<0.05$, statistical significance in the multivariable regression.
†The CHA2DS2-VASc score is a clinical estimation of the risk of stroke in patients with atrial fibrillation (congestive heart failure, hypertension, age >75 years, diabetes mellitus, prior stroke, vascular disease, age 65~75 years, female sex).

drugs for restroke prevention. Nonetheless, neurologists are staggering between the effectiveness of secondary stroke prevention and the risk of bleeding, often overestimating the bleeding risk.

The most devastating bleeding complication of OACs is intracerebral haemorrhage, which can cause even higher mortality than ischaemic stroke alone.[20 21] Although OAC treatment initiation post intracranial haemorrhage was proven to be feasible,[22] restarting antithrombotic drugs was very discreet and often underused.[23] In China, the fear of bleeding ranked top in the lists of reason for not prescribing OACs [9], which reflects the knowledge gap of neurology care on this dilemma.

In addition, a lack of knowledge about AF management, such as inappropriate interpretation of the CHA_2DS_2-VASc and HAS-BLED scores, often led to insufficient care by neurologists, both in Europe and China.[24 25]Consequently, education on the physician side to conduct guideline-directed medical therapy for AF-associated strokes is necessary.

Patient refusal is another reason accounting for the lower OAC prescription rate by neurology care facilities.[9] Previous studies have demonstrated that patients are more concerned about adverse reactions and are likely to refuse OAC therapy.[26] Meanwhile, patients with higher educational levels and more knowledge about OACs might be more compliant with anticoagulation therapy.[27] Educational interventions on patients, either by educational videos or doctors,[28] could improve OAC management and patient adherence.[29]

Through all the efforts for a decade, the OAC use has been improved. The overall anticoagulation rate in patients with previous strokes at discharge from early studies in China was 19.4%,[9] but increased to 53.66% in our study. However, this was still much lower than that of the Darlington study and Gulf Safe study,[4 5] which were 56.3% and 62%, respectively. Therefore, the room for further improvement is large. Efforts to reinforce education on neurologists, patients and patient relatives are imperative.

3. Promote the posthospital patient management system to improve prognosis

In our study, we reviewed the AF-related patient who had a stroke from a high-volume academic tertiary hospital after a median follow-up of 3 years after discharge. We found a higher loss of follow-up (11.92%), higher restroke rate (26.46%), higher mortality (31.69%), lower anticoagulation rate at discharge (53.66%) and lower medicine adherence (80.00% in NOACs and 77.32% in warfarin), compared with other coetaneous similar studies.[1–7 9] These results strongly suggest that lacking a 'post-discharge management' system is a great obstacle for improving long-term prophylaxis in AF-related patients who had a stroke. We therefore propose setting up a multiple disciplinary team to provide an integrated approach for the management of AF patients who had a stroke after discharge. Neurologists need to work with cardiologists to build up this platform and interact with community healthcare providers. This platform should also be supported by rehabilitation physicians. For each particular patient, evaluation of restroke risk, bleeding risk of OACs and cardiovascular comorbidities must be performed at the time of discharge. A long-term regimen should be decided, and regular follow-up should be performed. This complies with guideline-directed medical therapy and is in line with previous similar reports, such as 'the ABC Pathway' and 'the ALL-IN trial',[30 31] which allows the streamlining of integrated care for AF patients and show a clear benefit of improved outcomes.[31–33] Following the clinical pathways and interacting with cardiologists and neurologists, community healthcare providers should perform: (1) regular check-ups and monitoring of anticoagulation therapy; (2) routine education on patients and relatives; and (3) risk factor management and lifestyle change recommendations. Such a multiple disciplinary team and an integrated approach would definitely optimise the posthospital management of AF-related patients who had a stroke, thus improving the prognosis.

Limitations

First, this was a retrospective observational study from a large tertiary, provincial hospital. The results from our study might not represent real-world neurology care for secondary stroke prevention in all AF patients. However, we believe the real-world outcomes from all hospitals might be even worse. Second, the follow-up data were obtained by clinical visits and telephone interviews for those who were unable to visit. The accuracy of these results might be diluted, but the mortality, restroke rate and OAC adherence were reliable and the alarm is going off. Third, only one time follow-up was performed at the median of 3 years after discharge, the recall bias should be considered, especially in the OACs acceptance and adherence part.

CONCLUSIONS

As shown in figure 3, neurology care of AF-related patients who had a stroke is challenged in China by a lower AF detection rate, the significant underuse of OACs, poor OAC adherence and a lack of effective posthospital

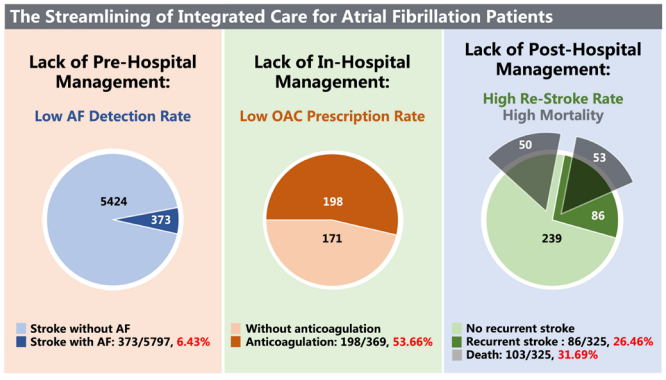

Figure 3 Central illustration figure of the study. AF, atrial fibrillation; OAC, oral anticoagulant.

management. Therefore, the overall restroke rate and the death rate are unexpectedly high. Strong measures should be taken, such as physician education, to adhere to guideline-directed medical therapy and standardisation of a posthospital management pathway to further improve the long-term outcomes in such a high-risk population.

Contributors MC was responsible for the project design, management, statistical analysis and overall write up. ZW and NW: project inception, questionnaire design, patients follow-up and write up. FW and ML conducted the statistical analysis and interpreted the findings. LZ and QW: neurological evaluation. XG and YY: data collection and patients follow-up. All contributed to this manuscript and approved the final draft. Guarantor: MC.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained from parent(s)/guardian(s).

Ethics approval This study involves human participants and was approved by Ethical committee of the First Affiliated Hospital of Nanjing Medical University, 2014-SR-113. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

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