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Optimal Thromboprophylaxis in Elderly Chinese Patients with Atrial Fibrillation (ChiOTEAf) registry: protocol for a prospective, observational nationwide cohort study

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Introduction Atrial fibrillation (AF) is a worldwide healthcare burden that is associated with the ageing population. Elderly patients with AF with multiple comorbidities usually present with a high risk of thromboembolism and bleeding. Limited prospective data are available from Asian cohorts on the epidemiology and complications of AF. The present prospective cohort study aims to explore contemporary antithrombotic strategies among the elderly Chinese population in the new era of non-vitamin K antagonist oral anticoagulants and to compare the clinical characteristics and outcomes between Chinese and European AF populations.

Methods and analysis The Optimal Thromboprophylaxis in Elderly Chinese Patients with Atrial Fibrillation (ChiOTEAf) registry will recruit 5000 patients with AF over 65 years of age in China. AF-related risks, including stroke/systemic thromboembolism and bleeding outcomes, will be assessed. Medical history, risk factors, demographic information and management will be collected at baseline, and clinical events during 1 year follow-up will be recorded. Follow-up will be conducted for at least 1 year and then annually thereafter. As our registry has a common protocol to the European Society of Cardiology EURObservational Research Programme AF general registry programme, preplanned analyses comparing the clinical profiles and outcomes will be performed. The ChiOTEAf registry offers an opportunity to provide a better understanding of the clinical profiles and adverse outcomes of patients with AF in China and allow for comparisons with a contemporary European population.

Ethics and dissemination Ethics approval was granted by the Central Medical Ethic Committee of Chinese PLA General Hospital (approval no S2014-065-01). The (inter)national research presentations, peer-reviewed publications and media coverage of the research will be sued for dissemination of the results.

Introduction Atrial fibrillation (AF) is evident as a worldwide epidemic in the 2013 WHO Global Burden of Disease database.¹ AF and its major complication, stroke/systemic thromboembolism, have a profound impact on disability and mortality, and the condition is particularly serious in the elderly population.²

The management of AF has had many updates and new developments over recent years,³–⁵ with the introduction of clinical risk scores (ie, Congestive heart failure, Hypertension, Age, Diabetes, Stroke(CHADS²); Congestive heart failure, Hypertension, Age ≥75, Diabetes, Stroke, Vascular disease, Age 65–74 and Sex category (female) (CHA₂DS₂VASC) and Hypertension, Abnormal renal/liver function, Stroke, Bleeding history, Labile international normalised ratio, Elderly, Drugs) and non-vitamin K antagonist oral anticoagulants (NOACs). Recent reports suggest that
approximately 80% of patients with AF in Europe and 55% of patients with AF in North America use oral anticoagulants.6,7 In China, the use of warfarin was only 7% as reported in the Chinese Society of Cardiology survey published in 20048 and 14% in the more recent 2013 study.9 Thus, we need more data on the contemporary management and treatment of AF in elderly Chinese patients in the new era of NOACs.

NOACs have shown advantages over warfarin for stroke prevention in pivotal randomised clinical trials (RCTs),10 with better efficacy and safety seen in Asian subgroups of those RCTs compared with non-Asians.11

Of note, Asians are more susceptible to haemorrhagic stroke, with a fourfold increased risk for intracranial haemorrhage associated with warfarin, when compared with the white population.12,13

The pattern of various comorbidities may differ between Asians and non-Asians, which may have implications for adverse outcomes related to this arrhythmia. For example, patients with AF who have atherosclerotic disease (ie, coronary artery disease (CAD) and peripheral artery disease (PAD)) have increased composite outcomes of cardiovascular death, myocardial infarction and stroke compared with patients with AF without atherosclerotic disease.14 This special population would benefit more from thromboprophylaxis, but they may be at higher risk for bleeding.15 The presence of PAD also seems to confer a particularly high risk of stroke in Asian patients with AF.16

The present prospective cohort study (Optimal Thromboprophylaxis in Elderly Chinese Patients with Atrial Fibrillation (ChiOTEAF) registry) aims to explore contemporary antithrombotic strategies among the elderly Chinese population in the new era of NOACs, and it focuses on the optimal antithrombotic therapy in patients with AF with high-risk factors. Second, we aim to compare the clinical characteristics and outcomes between the Chinese and European AF populations. The latter is possible as our registry has a common protocol to the European Society of Cardiology EURObservational Research Programme AF (EORP-AF) general registry programme, so preplanned analyses comparing the clinical profiles and outcomes will be performed.

Primary and secondary hypotheses

The primary hypothesis is to analyse the relationship between antithrombotic management of AF and cardiovascular events at 6 months and 12 months in the included patients with AF.

The secondary hypotheses are to explore the regional differences in antithrombotic therapies used, as well as adverse outcomes over follow-up, between the European and Chinese cohorts.

METHODS

The ChiOTEAF registry is a prospective, multicentre, observational registry. All of the patients will give written informed consent.
ischaemic attack, pulmonary embolism, deep vein thromboembolism, other thromboembolism (eg, peripheral embolism, atrial thrombus and left atrial appendage thrombus).

Haemorrhage events include intracranial haemorrhage and extracranial bleeding. Intracranial haemorrhage is defined as intracerebral haemorrhage, subarachnoid haemorrhage, acute subdural haematoma, chronic subdural haematoma, epidural haemorrhage and subdural haematoma. Major bleeding is defined as clinically overt bleeding accompanied by one or more of the following: a decrease in the blood haemoglobin level of more than 2.0 g/dL or more over a 24-hour period, the need for a transfusion of 2 or more units of packed red cells, the need for corrective surgery or bleeding at a critical site (extracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome or retroperitoneal).

ACS includes unstable angina, non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI). All-cause death includes cardiac death, vascular death and non-cardiovascular death. Cardiac death includes death caused by STEMI/NSTEMI, heart failure, arrhythmia, cardiac perforation/tamponade and other deaths of cardiac origin. Vascular death includes death ascribed to ischaemic stroke, haemorrhagic stroke, systemic bleeding, peripheral embolism and pulmonary embolism.

**Study setting and site selection**

Mainly cardiologists, together with specialists in neurology and surgeons, were invited to participate in the study. Site selection is designed to provide a distribution across regions in China so it is representative of the Chinese AF population. Study sites were selected among hospitals in China that would provide good quality medical services and correct corresponding diagnoses. A pilot investigation was initially carried out to obtain general information on the rate of patients with AF by age in the possible sites before the full ChiOTREAF registry commenced. The investigation showed that the distribution rates of AF were approximately 15%, 18%, 44% and 23% in the age groups of 50–64 years, 65–74 years, 75–84 years and over 85 years, respectively. Study sites were selected based on the pilot investigation and site quality. In total, 44 sites from 20 provinces are involved in the present registry study.

**Data management**

All of the site data will be collected locally and forwarded to the central clinical research database. The database will be monitored in real time by a data management centre. Data management for the ChiOTREAF registry will be performed by an independent third party (Westat, Rockville, Maryland, USA). The independent third-party audit will mainly monitor the following points: health, safety and that the relevant rights of subjects are protected; the sites carry out the study according to protocol; the data collected are true and accurate and the site staff and facility meet the protocol requirements.

**Statistical approach**

Data will be summarised using mean (SD), medians (range) for continuous data and counts (percentages)
for categorical data. Continuous variables will be tested for distribution by the Kolmogorov-Smirnov test. Those with a normal distribution will be presented as a mean with SD and analysed by t-test or Analysis of Variance test. Data with a non-normal distribution will be presented as median with IQR and will be analysed by non-parametric methods. The comparison of discrete variables will be performed via the X² test. A Cox proportional hazard model on the outcomes will be performed to test the impact of covariates (patient characteristics, physician characteristics, risk scores and antithrombotic drugs). The analysis will be conducted for age groups, particularly for patients ≥75 years old to clarify the association between age and outcomes. All of the statistical analyses will be considered significant at the 5% confidence limit using two-sided tests or two-sided CIs.

Planned analyses include the following:

- description of patient characteristics and risk factors at baseline, changes in the thromboembolic/bleeding risk profiles and changes in the antithrombotic treatment during follow-up, as well as compliance of antithrombotic therapy related to the risk assessment;
- evaluation of the 6-month and 12-month cardiovascular event rates (stroke, systemic thromboembolism, major bleeding and cardiovascular death) in relation to different antithrombotic therapies used for the AF population;
- comparison of clinical features, use of oral anticoagulation therapies and clinical outcomes between patients with AF in Europe and those in China.

**Determination of sample size**

Assuming an annual rate of stroke/systemic thromboembolism of 6.0% in the non-anticoagulated AF population compared with 2.0% in anticoagulated patients, we will need n=424 anticoagulated patients to test a difference in outcome, with a power of 80% and 1−α=0.05. Assuming the rate of anticoagulant use is 30% in the population, we will need 1413 patients. The withdrawal rate is assumed to be 10% during the first year, thus the sample size for this study will need to be at least 1554 patients with 1 year follow-up to show a crude difference with anticoagulant use. Nevertheless, the present study is observational, and some patients will be recruited to allow us to have sufficient information on subgroups of patients to do further analysis. Hence, an estimated sample size of 5000 enrolled patients is required.

**DISCUSSION**

The ChiOTEAF registry will update the clinical epidemiology of AF in the current era of NOACs, clarify the current antithrombotic strategies used in China and compare AF management between Western and Chinese populations.

Clinical epidemiological studies on AF in China over the past decades have demonstrated that the rate of warfarin use was low, with 2.7%–21.2% in community-based studies and 6.7%–18% in hospital-based studies, whereas the reported rates of stroke/thromboembolism ranged from 4.1% to 17.5% (table 2). More recently, various international studies involving Asia showed a much higher rate of anticoagulant use in those countries, between 35% and 55% (table 3). Nevertheless, the current profile of anticoagulant management remains unclear in China, especially since the availability of NOACs has changed the landscape of AF management worldwide. Updated information on AF management in China is needed given the huge AF burden in the world’s most populous country.

Although RCTs have confirmed the safety of NOACs, many issues need to be addressed in ‘real-world’ practice, such as gastrointestinal bleeding. Indeed, elderly patients are usually at high risk of both thromboembolism and bleeding. The ChiOTEAF registry provides an opportunity to observe the effectiveness and safety of NOACs in a high-risk Chinese population. Furthermore, cardiovascular risk factors are changing over time. For example, vascular disease (myocardial infarction and peripheral vascular disease) is an independent risk factor that contributes to the stroke/thromboembolism. In several observational AF cohorts, 19%–47% of patients with AF have CAD and 6%–11% have PAD. The prevalence of atherosclerotic vascular disease is more common in elderly patients.

A treatment gap of AF management exists between Western and Eastern populations despite advances in AF management. The direct comparison of Western and Eastern populations from different studies published thus far cannot be reliably performed due to different study designs. While limited studies have investigated ethnic differences across different countries, even the international registry studies involving different countries have not been designed to reveal the differences (table 3).

The ChiOTEAF registry is designed to have aligned definitions of clinical features and comorbidities with a common case report form (CRF) and protocol with the EORP-AF registry, which makes the two registries comparable. EORP-AF and ChiOTEAF are two independent contemporary registries, carried out in Europe and China, respectively. Thus, differences in AF management can be compared and analysed in Western and Chinese populations, which is a preplanned analysis. With the aligned definitions, the ChiOTEAF registry could also be potentially compared with similar registries conducted in Iran and by the Asia Pacific Heart Rhythm Society using the EORP-AF protocol and CRF. Thus, this novel study design cannot only investigate the clinical epidemiology of China, but it can also make the direct comparison among different country/regional populations practical.

**Limitations**

The ChiOTEAF registry is an observational, real-world cohort study. The AF population will be recruited across China, but as possible limitations common to observational cohort studies, inadequacy of data recording/capture and selection bias may occur. To avoid this as
### Table 2  Clinical epidemiology of atrial fibrillation in China

| Author et al. | Study date/place | Design/patients | AF prevalence/ incidence | Warfarin, % | Aspirin, % | Stroke prevalence, % |
|---------------|------------------|-----------------|--------------------------|-------------|-------------|---------------------|
| Zhou and Hu17 | 2003             | China mainland: prospective, cross-sectional n=29079 Age ≥30 years | Overall: 0.77% Male: 0.91% Female: 0.63% | 2.7% | 39.7% | 12.9% |
| Zhang et al18 | 2004             | China mainland: prospective, random cluster sampling n=18615 Age ≥35 years | Overall: 1.04% Male: 1.09% Female: 1.00% | – | – | 13.4% |
| Long et al18  | 2003-2006        | China mainland: prospective, cross-sectional n=19964 Age ≥55 years | Overall: 0.80% Male: 1.15% Female: 0.66% | – | – | – |
| Mu et al20    | 2009             | China mainland: prospective n=30000 Mean age 50.5 (30.5) years | Overall: 2.83% Male: 5.66% Female: 2.87% | – | – | – |
| Guo et al21   | 2001–2012 with follow-up for 11 years/China mainland | Retrospective, n=471446 Age ≥20 years | Prevalence: Overall: 4.1% Male: 0.27% Female: 0.28% Incidence: Overall: 0.05/100 person-years | 32.3% | – | Annual stroke rate: 6% |
| Li et al22    | 2006–2011 with a median 3.8 years of follow-up | Prospective, n=4750 Age ≥62 years | Incidence: Overall: 1.0% Male: 4.8% Female: –| – | – | – |
| Chien et al23 | 1990–2000, with follow-up of 9 years | Taiwan: prospective n=3580 Age ≥35 years | Overall: 1.07% Male: 1.4% Female: 0.7% | – | – | Prior stroke rate: 2.6% |
| Lin et al24   | July 2003–June 2004 | Taiwan: retrospective; data from the Taiwanese National Health Insurance medical claims databases n=39541 Mean age 70±12.1 years | – | 21.2% | 46.7% | Previous thromboembolism, 15.0% |
| Society of Cardiology, Chinese Medical Association25 | 1999–2001 | China mainland: retrospective n=9297 Age 18–99 years | Incidence: 7.9% per year | 6.6% | 57.9% | 17.5% |
| Sun et al; Hu et al26 | January 2000–April 2002 | China mainland: retrospective; n=3425 (with NVAF) | – | 9.1% | 56% | 16.4% |
| Guo et al27   | January 1995–May 2015, with the observational period of 20 years | China mainland: retrospective; n=4824 Mean age 67 years | – | 9.33% | 21.19% | 7.38% |
| Guo et al28   | November 2007–July 2010, with follow-up of 1.9 years | China mainland: retrospective cohort study; n=1034 Median age 75 years | – | 14% | Aspirin: 39.3% Clopidogrel: 10.7% Aspirin+clopidogrel: 21.5% | Annual stroke/thromboembolism rate: 4.5% |
| Yang et al29  | November 2008–October 2011, with follow-up of 1 year | China mainland: prospective cohort study; n=2016 Median age 68 years | – | 18% | – | 7.40% |

Continued
much as possible, site selection will be carried out among 2A and 3A Grade hospitals in China, which would guarantee a similarly high quality of medical services. In addition, the site selection was partly based on the pilot investigation, which will further be confirmed by data monitoring by a third-party contract research organisation through individual site assessment visits.

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Table 2 Continued

| Author | Study date/place | Design/patients | AF prevalence/ incidence | Warfarin, % | Aspirin, % | Stroke prevalence, % |
|--------|------------------|-----------------|--------------------------|-------------|-------------|----------------------|
| Li et al28 | January 2008– December 2014 | Hong Kong: retrospective; n=2099 Mean age 73 years | – | Warfarin: 45.9% Rivaroxaban: 31.9% Dabigatran: 22.2% | – | Annual stroke incidence: 4.10%/year |
| Lee et al29 | 1997–2002 | Taiwan: retrospective n=162340 Mean age 73 years | Overall incidence: Annual mean 127 per 100000 Male: 137 per 100000 Female: 116 per 100000 | – | – | Prior stroke: 15% |

AF, atrial fibrillation; NVAF, non-valvular atrial fibrillation.

Table 3 International studies of atrial fibrillation (including Asian/China subgroups)

| Author | Study date | Patients | Ethnicity, n, % | OACs, % | Aspirin, % | Stroke prevalence, % |
|--------|------------|----------|----------------|---------|-----------|----------------------|
| Ohman et al20,31 | RecordAF, RecordAF-Asia Pacific, with 1 year follow-up April 2009–July 2010 | n=5604 Mean age 66 years n=2629 Mean age 64 years | RecordAF-Asia Pacific: Chinese: 951 (36%) Korean: 453 (17%) White: 446 (17%) Thai: 515 (20%) Other: 264 (10%) | RecordAF: 52% RecordAF-Asia Pacific: 36% | – | RecordAF 2.1% RecordAF-Asia Pacific: |
| Ohman et al6 | REACH registry, with 4 years outcome 2003–2009 | n=4582 Mean age 64 years | – | North America/ South America: 59.8% Western Europe/ Eastern Europe: 51.8% Asia/Japan/Middle East: 44.6% | 48.9% | 7.7% |
| Oh et al32 | GARFIELD registry 2010–2013 | n=17162 Asia: mean age 61 years Other regions: mean age 71 years | Other regions of the world: 13541 (78.9%) Asian: 3621 (21.1%) | Other regions of the world: – Asian: 37.8% | – | – |
| Huisman et al33 | GLORIA II November 2011– December 2014 | n=15092 Mean age 71 years | Europe: 7108 (47.1%) North America: 3403 (22.5%) Asia: 3071 (20.3%) Latin America: 913 (6.0%) Middle East/Africa: 597 (4.0%) | Europe: 90.1% North America: 78.4% Asia: 55.2% Latin America: 85.3% Middle East/Africa: 87.4% | Europe: 6.0% North America: 14.0% Asia: 25.1% Latin America: 10.5% Middle East/Africa: 11.1% | – |

OAC, oral anticoagulant.
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Contributors YG and GYHL had the main idea of the study and drafted the manuscript. YW, XL, ZS, XS and GX contributed to the design of the study and were involved in the editing of the manuscript. All of the authors have read and approved the final manuscript.

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Patient consent Obtained.

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