MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2019; 25: 4691-4698
DOI: 10.12659/MSM.917131

Received: 2019.04.22
Accepted: 2019.06.03
Published: 2019.06.24

Control of Anticoagulation Therapy in Patients with Atrial Fibrillation Treated with Warfarin: A Study from the Chinese Atrial Fibrillation Registry

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF 1,2 Hai-Feng Liang
ADEF 1 Xin Du
CD 3 Ying-Chun Zhou
BC 3 Xiao-Yi Yang
BF 1 Shi-Jun Xia
BDF 1 Jian-Zeng Dong
ADEF 4,5 Gregory Y.H. Lip*
ABCEFG 1 Chang-Sheng Ma

1 Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University, National Clinical Research Center for Cardiovascular Diseases, Beijing, P.R. China
2 Department of Cardiology, Fuxing Hospital, Capital Medical University, Beijing, P.R. China
3 East China Normal University, Shanghai, P.R. China
4 Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart and Chest Hospital, Liverpool, United Kingdom
5 Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

* Chang-Sheng Ma and Gregory Y.H. Lip are co-senior authors

Corresponding Author: Chang-Sheng Ma, e-mail: chshma@vip.sina.com

Source of support: This study was supported by grants (2013BAI09B02 and2013DFB30310) from the Ministry of Science and Technology of the People's Republic of China and grants (D111100003011004 and D131100002313001) from Beijing Municipal Commission of Science and Technology and Beijing Municipal Administration of Hospitals Clinical Medicine Development of Special Funding Support (code: ZYLX201302). The Chinese Atrial Fibrillation Registry study was funded by Bristol-Myers Squibb, Pfizer, Johnson & Johnson, Boehringer Ingelheim, and Bayer

Background: Several factors determine the efficacy of warfarin anticoagulation in patients with non-valvular atrial fibrillation (NVAF). This study aimed to use data from the Chinese Atrial Fibrillation Registry study to assess the control of anticoagulation therapy in Chinese patients with NVAF treated with warfarin.

Material/Methods: From the Chinese Atrial Fibrillation Registry study the anticoagulant use and dosing, the time in therapeutic range (TTR) of the international normalized ratio (INR), and standard deviation of the observed INR values (SD_{INR}), and their influencing factors were evaluated.

Results: The median INR and SD_{INR} were 2.04 (IQR 1.71–2.41) and 0.50 (IQR, 0.35–0.69), respectively. The median TTR was 51.7% (IQR, 30.6–70.1%) and only 25.1% had a TTR ≥70%. Age was ≥70 years (OR, 0.72; 95% CI, 0.55–0.94; P=0.015), bleeding history (OR 0.48; 95% CI, 0.23–0.89; P=0.029), the use of a single drug (OR, 0.62; 95% CI, 0.42–0.92; P=0.016), more than drug (OR, 0.60; 95% CI, 0.41–0.88; P=0.009), and lack of assessment of bleeding risk (OR, 0.72; 95% CI, 0.54–0.97; P=0.033) were associated with TTR <70% (INR 2.0–3.0). Coronary heart disease (CHD) and peripheral artery disease (PAD) (OR, 0.69; 95% CI, 0.52–0.90; P=0.007) and diabetes mellitus (OR, 0.79; 95% CI, 0.62–0.99; P=0.044) were associated with increased variability in INR (SD_{INR} ≥0.5).

Conclusions: In Chinese patients with NVAF, warfarin anticoagulation was associated with lower TTR and less stable anticoagulation than in current guidelines, and risk factors for reduced safety and efficacy were identified.

MeSH Keywords: Anticoagulants • Atrial Fibrillation • Quality Control • Warfarin

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/917131

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Background

The vitamin K antagonists that include warfarin are highly effective for the prevention of stroke in patients with atrial fibrillation (AF) [1]. An appropriate degree of anticoagulant and maintenance of stable anticoagulation are important in balancing the benefits of warfarin in the prevention of stroke and in avoiding the risk of bleeding [2]. It is has been assumed that Asian populations are at a higher risk of bleeding when treated with warfarin [3]. The Chinese Atrial Fibrillation Registry study is a hospital-based, multicenter, prospective registry study, that includes real-world data of approximately 20,000 patients with AF [4]. An international normalized ratio (INR) target range of 2.0–3.0 is recommended by the Chinese Atrial Fibrillation Registry management guidelines [4], and an INR range of 1.6–2.6 has been recommended for patients with AF who are ≥70 years old by the Japanese Circulation Society [5,6].

In China, there are limited data on the degree of anticoagulation required in real-world clinical practice and on the factors that influence the effectiveness of anticoagulation. In this study, we identified patients with nonvalvular atrial fibrillation (NVAF) taking long-term warfarin therapy from the Chinese Atrial Fibrillation Registry study. Quality of anticoagulation control as reflected by time in therapeutic range (TTR) of the international normalized ratio (INR) and anticoagulation stability, or the standard deviation of INR (SD_{INR}), were evaluated [7,8]. Factors associated with TTR ≥70% and anticoagulation stability were also analyzed. This study aimed to use data from the Chinese Atrial Fibrillation Registry study to assess the control of anticoagulation therapy in Chinese patients with NVAF treated with warfarin.

Material and Methods

Study population

The Chinese Atrial Fibrillation Registry study is a prospective, multicenter, hospital-based, ongoing registry study of patients with atrial fibrillation (AF) in Beijing, China [4]. Thirty-one tertiary and non-tertiary hospitals in Beijing that treated patients with AF were included in the study [9]. Each patient signed an informed consent before enrolment. We extracted the data of patients with AF treated with warfarin from the Chinese Atrial Fibrillation Registry study from August 1, 2011, to June 30, 2016 [4]. Exclusion criteria included age <18 years, rheumatic valvular disease, others diseases with life expectancy <6 months, with anticoagulation therapy other than warfarin, number of INR values <5, the maximal interval between two successive INR values >90 days and follow-up period of more than six months. The INR values of the first six weeks of the patients who had recently commenced treatment with warfarin were excluded.

Data collection

Relevant information about warfarin treatment, including the date of starting and stopping warfarin, and all INR values during the time period were collected. To minimize missing data, INR values from the hospital information system (HIS) of participating hospitals were extracted and integrated with those from Chinese Atrial Fibrillation Registry database.

Baseline information included demographic characteristics including age, gender, history of smoking, alcohol consumption, comorbidities that included hypertension, diabetes mellitus, heart failure, stroke, transient ischemic attack (TIA), thromboembolism, peripheral artery disease (PAD), bleeding history, and coronary heart disease (CHD), was collected. Patients were followed up in the third month, sixth month, and every six months after that. Data were collected on the use of antiplatelet agents and other concomitant drugs, including antiarrhythmic drugs, drugs to control ventricular rate, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and statins.

Ethics

This study was approved by the Beijing Anzhen Hospital Ethics Committee (No. D11110700300000) on June 10, 2011.

Quality of anticoagulation control and stability of warfarin

The time in the different therapeutic range of INR (TTR) was calculated using the Rosendaal method [10]. TTR ≥70% was considered as high-quality INR control according to the European Society of Cardiology (ESC) guidelines [7]. The distribution of TTR and INR reflected the quality of anticoagulation control in the warfarin-treated patients. Anticoagulation stability was assessed using the standard deviation (SD) of observed INR values (SD_{INR}) of each participating patient [8]. In this study, SD_{INR} <median (0.5) was considered as high anticoagulation stability.

Definitions

A score for bleeding risk was derived from the Atrial Fibrillation Effect on Quality-of-life (AFEQT) score [11]. The risk of bleeding was scored on a 1–7 Likert scale (ranging from 1, not at all, to 7, extremely). We defined 1–2, 3, and 4–7 as low, moderate, and high levels of bleeding risk, respectively. The risk of stroke for each patient was evaluated using the CHA_2DS_2-VASc score, which included congestive heart failure, hypertension, diabetes mellitus, vascular disease including coronary heart disease (CHD) or peripheral arterial disease (PAD), female gender, and age between 64–75 years contributed 1 point and 2 points each for stroke, TIA, thromboembolism history and age ≥75 years [12–14].

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

HAS-BLED was used as a scoring system for bleeding risk with 1 point (range, 0–9) assigned for the presence of each of the following: old age, hypertension, abnormal liver or renal function, a previous stroke, a history of bleeding, unstable INRs, concomitant drugs or alcohol excess [15]. A HAS-BLED score of ≥3 indicated an increased risk of bleeding [15].

SAMe-TT_2R_2 score was calculated using the factors of female gender, age (<60 years), medical history, with at least two of the following: hypertension, diabetes mellitus, CHD, PAD, congestive heart failure, stroke history, pulmonary disease, hepatic or renal disease. Treatment, with interacting drugs such as amiodarone, contributed 1 point respectively and 2 points each for current tobacco use and race (non-Caucasian) [16].

Statistical analysis

Continuous variables were reported as the mean ± standard deviation (SD), or the median (IQR 25–75%), and categorical variables as n (%). A multivariate logistic regression model was constructed to identify the associated factors independently associated with the degree of anticoagulation and stability. In the model, we adjusted age, gender, history of stroke, TIA, thromboembolism, history of bleeding, history of myocardial infarction, known CHD or PAD, diabetes mellitus, hypertension, congestive heart failure, anemia, combined platelet agents, current smoking, current drinking, bleeding risk score, combination medication, CHA_2DS_2-VASc score and HAS-BLED score. Data were analyzed using SAS version 9.2 software. P<0.05 was considered to be statistically significant.

Results

A total of 1,895 eligible patients with a mean age of 66.78±9.60 years (56.5% were men) who were treated with warfarin were included in this study. Only 24.8% of patients with non-valvular atrial fibrillation (NVAF) in the Chinese Atrial Fibrillation Registry met the inclusion criteria for this study. The patient inclusion process for this study is shown in Figure 1. Baseline characteristics of the included patients are shown in Table 1.

Distribution of the international normalized ratio (INR) values

We collected 29,335 international normalized ratio (INR) values during a median follow-up time of 1,094 days (IQR, 729–1,609 days). The median interval of INR testing was 29 days (IQR, 23–38 days). The number of INR tests for each patient ranged from 5–114, with a median of 9 (IQR, 6–18). INR values ranged from 0.69–19.85, with a median of 2.04 (range, 1.7–2.4). The density distribution of INRs is shown in Figure 2.

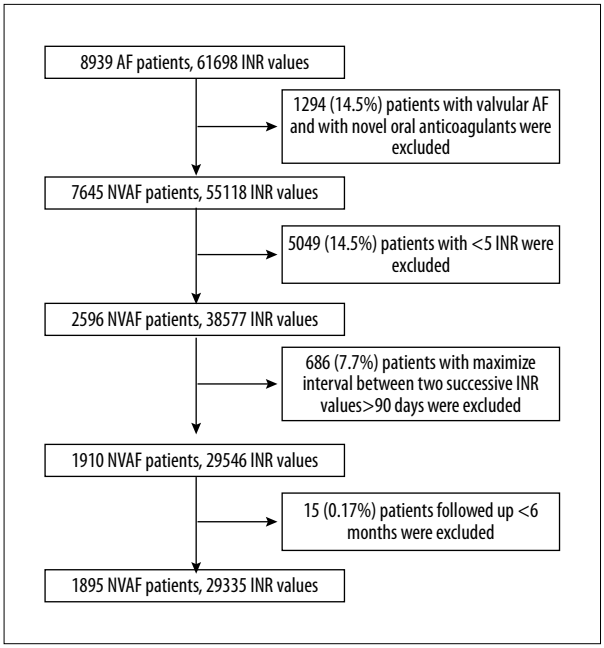

Figure 1. Flowchart of the patient recruitment in this study.

When the INR target range was set as 2.0–3.0, only 475 patients (25.1%) had a TTR ≥70%, and 724 patients (38.2%) had a TTR ≥60%. The median TTR was 51.7% (IQR, 30.6–70.1%)]. The mean time distribution of the INR under the low boundary of therapeutic range (INR <2.0) was significantly higher than that above the upper boundary of the therapeutic range (INR >3.0) [42.0% (IQR, 22.5–65.0%) versus 0.33% (IQR, 0.0–5.8%), p<0.01], the median time distributions of INR <2.0 were 44.90±28.18% versus 5.07±9.82% for INR >3.0 (p<0.01).

With regard to different INR ranges of <1.6, 1.6–2.0, 2.0–2.6, 2.6–3, and ≥3, the time distributions of INR were not significantly different in the different patient subgroups (<70 years or ≥70 years, female or male, with or without history of stroke, TIA, or thromboembolism, with or without history of bleeding, CHA_2DS_2-VASc score <2 or ≥2, HAS-BLED score 0–2 or >2 (all, P>0.05).

If we set the INR target range as 1.6–2.6, 1123 (59.3%) patients had a TTR ≥70%. The median TTR was 75.2% (IQR, 57.0–88.3%), significantly higher than the proportion when INR target range was set as 2.0–3.0, with a median of 51.7% (IQR, 30.6–70.1%) (p<0.0001) (Figure 3).

Variability of anticoagulation intensity

The median SD_{INR} was 0.50 (IQR, 0.35–0.69). The SD_{INR} was not significantly different in subgroups of age <70 or ≥70 years, male and female, with or without a history of stroke, TIA, or thromboembolism and bleeding, higher or lower bleeding risk score, CHA_2DS_2-VASc score and HAS-BLED score (all, P>0.05) (Supplementary Table 1).

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Table 1. Patient characteristics.

Characteristics	Total (N=1895)
Age, (y)	66.78±9.60
Male	1071 (56.5)
Current drinking*	336/1886 (17.8)
Current smoking*	235/1886 (12.5)
Atrial fibrillation type	
Newly diagnosed	91 (4.8)
Paroxysmal	853 (45.0)
Persistent	951 (50.2)
Comorbidities	
Congestive heart failure	287 (15.1)
Hypertension	1331 (70.2)
Diabetes mellitus	535 (28.2)
Stroke/TIA/thromboembolism	456 (24.1)
Anemia	60 (3.2)
Prior MI/known CHD/PAD	337 (17.8)
Chronic kidney disease	7 (0.4)
Bleeding history	109 (5.8)
Medication	
Antiplatelet agents	334 (17.6)
Antiarrhythmic drugs	476 (25.1)
Rate control drugs	1210 (63.9)
ACEI/ARB	770 (40.6)
Statin	785 (41.4)
Score	
Bleeding risk	3.11±1.00
CHA_2DS_2-VASc score	3.09±1.71
HAS-BLED score	2.60±1.15
SAMe-TT2R2 score	3.64±1.07

Data were indicated as mean ± standard deviation (SD) of the number (%); * N of total, 1886; N of age <70 years, 1068; N of age ≥70 years, 818. Angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs). TIA – transient ischemic attack; MI – myocardial infarction; CHD – coronary heart disease; PAD – peripheral artery disease.

Factors associated with anticoagulation intensity and stability

Multivariate logistic regression showed that for INR target range of 2.0–3.0, age ≥70 years, history of bleeding, low bleeding risk score, and concomitant drugs were independently associated with a TTR <70%. When the INR target range was 1.6–2.6, these factors were no longer significantly related to the TTR (Table 2). Multivariate logistic regression analysis showed that a history of myocardial infarction, CHD, PAD, and diabetes mellitus resulted in worse INR stability (SD_{INR} ≥0.5) (Table 3).

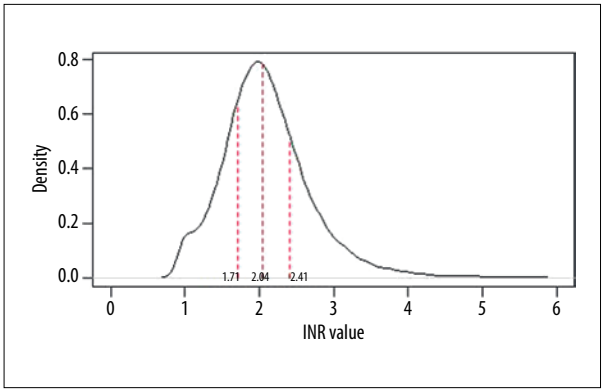

Figure 2. Distribution of the international normalized ratio (INR) in 1,895 patients with non-valvular atrial fibrillation (NVAF) treated with warfarin. Density: frequency/distance=percent/0.1. IQR – interquartile range.

Discussion

This study used data from the Chinese Atrial Fibrillation Registry study to assess the control of anticoagulation therapy in patients with non-valvular atrial fibrillation (NVAF) treated with warfarin. The distribution of the international normalized ratio (INR) values and the mean time in therapeutic range (TTR) showed that the quality of anticoagulation control was generally suboptimal. Also, for the INR target range of 2.0–3.0, age ≥70 years, history of bleeding, low bleeding risk score, and concomitant drugs were independently associated with a TTR <70%. The variability in INR was significantly associated with a history of coronary heart disease (CHD), peripheral arterial disease (PAD), and diabetes mellitus.

From this study, warfarin anticoagulation intensity was shifted towards lower INR ranges, with a median INR of 2.04, and the median time distribution proportion of INR <2 was more than 40%, compared with an INR >3 (less than 1%), the mean time distribution proportion were 44.90% and 5.07%. In the ROCKET AF trial, the mean time distribution proportion under the INR range <2 and >3 accounted for 29.1% and 15.7%, respectively [2]. Time distribution proportion of INR had the same tendency to each subgroup whether categorized by age, gender, history of stroke or transient ischemic attack (TIA), pulmonary embolism, bleeding history, CHA_2DS_2-VASc score, or HAS-BLED score, suggesting that the status of anticoagulation intensity that was shifted to left did not vary based on thromboembolic or bleeding risk. However, the CHA_2DS_2-VASc score and

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

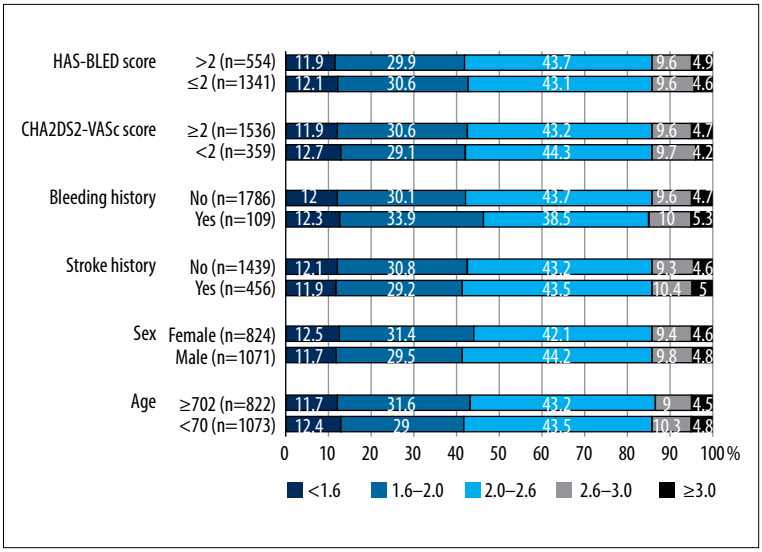

Figure 3. The comparison of the proportion of time of the international normalized ratio (INR) within subgroups, the HAS-BLED score, the CHA2DS2-VASc score, history of bleeding, stroke, transient ischemic attack (TIA), history of thromboembolism, gender, and age ($p<0.05$).

Table 2. Multivariate logistic regression analysis of factors associated with the time in therapeutic range (TTR) ≥70% with different international normalized ratio (INR) target ranges.

Characteristics	INR Target ranges of 2.0-3.0			INR Target range of 1.6-2.6		
	n/N (%)	O R(95% CI)	P value	n/N(%)	OR(95% CI)	P value
Age ≥70 y	177/822	0.72 (0.55–0.94)	0.015	473/822	0.93 (0.73–1.17)	0.531
Male	274/1071	0.96 (0.74–1.26)	0.786	654/1071	1.16 (0.92–1.46)	0.224
Stroke/TIA/thromboembolism	115/456	1.05 (0.74–1.48)	0.798	274/456	1.14 (0.84–1.56)	0.393
Bleeding history	16/109	0.48 (0.23–0.89)	0.029	64/109	0.95 (0.59–1.53)	0.824
Prior MI/known CHD/PAD	84/337	1.16 (0.84–1.57)	0.361	207/337	1.11 (0.84–1.47)	0.458
Diabetes mellitus	137/535	1.05 (0.8–1.36)	0.737	337/535	1.17 (0.92–1.49)	0.195
Hypertension	336/1331	1.27 (0.93–1.75)	0.13	775/1331	0.95 (0.72–1.25)	0.704
Congestive heart failure	60/287	0.83 (0.58–1.17)	0.285	174/287	1.11 (0.83–1.51)	0.483
Anemia	14/60	0.97 (0.48–1.84)	0.931	30/60	0.68 (0.39–1.2)	0.184
Combined platelet agents	82/334	1.07 (0.73–1.55)	0.739	195/334	1.07 (0.77–1.5)	0.675
Current smoking	67/336	1.08 (0.74–1.56)	0.679	137/235	0.81 (0.58–1.15)	0.236
Current drinking	93/235	1.1 (0.76–1.59)	0.603	209/336	1.27 (0.91–1.77)	0.165
Bleeding risk score <3	81/373	0.72 (0.54–0.97)	0.033	220/373	0.97 (0.75–1.26)	0.834
Bleeding risk score >3	95/395	0.82 (0.62–1.09)	0.178	226/395	0.91 (0.71–1.17)	0.456
*Concomitant drug (n=1)	128/527	0.62 (0.42–0.92)	0.016	327/527	1.24 (0.86–1.79)	0.243
*Concomitant drugs (n≥2)	284/1169	0.6 (0.41–0.88)	0.009	680/1169	0.93 (0.65–1.32)	0.694
CHA2DS2 –VASc score ≥2	376/1536	1.05 (0.71–1.55)	0.806	907/1536	1.09 (0.77–1.53)	0.639
**HAS-BLED score >2	132/554	0.95 (0.64–1.43)	0.821	319/554	0.85 (0.6–1.22)	0.379

* Concomitant drugs include antiarrhythmic drugs, ventricular rate control drugs, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and statins. ** Excluding labile INR. Total number=1895. Total number of TTR ≥70%=475 (INR range, 2.0–3.0). Total number of TTR ≥70%=1123 (INR range, 1.6–2.6). TIA – transient ischemic attack; MI – myocardial infarction; CHD – coronary heart disease; PAD – peripheral artery disease.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Table 3. Multivariate analysis of associate factors of SD_{INR} <0.5.

Characteristics	n/N(%)	OR (95% CI)	P value
Age ≥70 y	424/822	1.08 (0.85–1.36)	0.541
Male	533/1071	1.12 (0.89–1.41)	0.342
Stroke/TIA/TE	229/456	1.20 (0.88–1.62)	0.244
Bleeding history	54/109	0.98 (0.61–1.58)	0.946
Prior MI/known CHD/PAD	141/337	0.69 (0.52–0.90)	0.007
Diabetes mellitus	242/535	0.79 (0.62–0.99)	0.044
Hypertension	661/1331	1.23 (0.94–1.62)	0.135
Congestive heart failure	124/287	0.88 (0.66–1.18)	0.404
Anemia	26/60	0.97 (0.55–1.7)	0.908
Combined antiplatelet agents	152/334	1.05 (0.76–1.46)	0.765
Current smoking	121/336	1.25 (0.89–1.75)	0.196
Current drinking	158/235	0.87 (0.63–1.2)	0.39
Bleeding risk score <3	177/373	0.86 (0.66–1.1)	0.223
Bleeding risk score >3	203/395	1.03 (0.8–1.32)	0.817
*Concomitant drug (n=1)	269/527	0.79 (0.55–1.13)	0.204
*Concomitant drugs (n≥2)	564/1169	0.84 (0.59–1.2)	0.341
CHA2DS2 –VASc score ≥2	755/1536	1.05 (0.75–1.48)	0.772
**HAS-BLED score >2	261/554	0.76 (0.53–1.07)	0.119

* Concomitant drugs include antiarrhythmic drugs, ventricular rate control drugs, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and statins. ** Excluding labile INR. Total number of SD_{INR} <0.5=940. TIA – transient ischemic attack; MI – myocardial infarction; CHD – coronary heart disease; PAD – peripheral artery disease.

HAS-BLED scores were not associated with the degree of anticoagulation. Physicians do not often treat patients based on their risk [17–19]. Notably, the median INR in our study was 2.04, which was close to the recommended INR target range of 1.6–2.6 for patient age ≥70 years by the Japanese Circulation Society [5,6], although guidelines from China recommend the INR target range should be 2.0–3.0. The optimal INR range for warfarin use is debated in Asian populations because of the limited evidence from controlled studies [20]. It has been believed that Asian patients have an increased risk of hemorrhage because of race, genetics, and lifestyle differences [21]. Therefore, both physicians and patients appear more concerned about bleeding risk related to warfarin anticoagulation and aim for lower INR ranges. However, the TTR is a stronger determinant of bleeding risk than the INR values [22,23].

In this study, multivariate logistic regression analysis showed that age ≥70 years and bleeding history were independent risk factors associated with TTR. Reduced concern regarding the risk of bleeding may increase the compliance with and the effectiveness of anticoagulation. Therefore, patients undergoing warfarin anticoagulation therapy require education and support to improve their compliance with optimal anticoagulation therapy. Concomitant drug use is also independently associated with TTR, and is probably related to the interaction of various drugs in the body.

As this study showed, the standard deviation (SD) of observed INR values (SD_{INR}) is an important index of the INR variability, reflecting INR fluctuations, either outside or within the therapeutic window. The variability of INR is an important factor associated with the anticoagulation effects of warfarin, which is related directly to prognosis in patients on warfarin therapy [8,24,25]. In this study, INR fluctuation was associated with the patient history of CHD, PAD, and diabetes mellitus, which suggested these comorbidities significantly impacted the stability of anticoagulation. Attention to these comorbidities as part of a holistic and integrated approach to the management of AF would improve clinical outcomes [26–28].

The results of the present study showed that the quality of anticoagulation control using warfarin was suboptimal and this was associated with several factors that included age, comorbidities, concomitant drugs, and the attitudes of the physician and patient. It has been assumed that the stability of warfarin anticoagulation in Asian patients is worse than in European

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

and American patients [21]. The use of a clinical score helped to identify patients with AF who were less likely to do well on warfarin and included the SAMe-TT_2R_2 score, which in non-Caucasians was assigned 2 points [16]. Those patients with a SAMe-TT_2R_2 score ≥2 may require additional methods to improve the effects of anticoagulation, such as more frequent INR checks, education, and counseling [29].

Whether vitamin K antagonists or new oral anticoagulants (NOACs) are used, medication adherence is central to the prevention of thromboembolism. Although the use of NOACs is increasing, patients with valvular heart diseases and a high proportion of patients with non-valvular AF will still be on warfarin in China. Therefore, a multidisciplinary approach, including education of healthcare professionals, implementation of local guidelines, multidisciplinary medical care programs, and healthcare system support are needed to improve the quality of anticoagulant control [30,31].

This study had several limitations. First, Chinese patients with AF on long-term warfarin were identified from the Chinese Atrial Fibrillation Registry study [4]. It may be difficult to apply the findings from this study to other regions of China, as the Chinese Atrial Fibrillation Registry study mainly registered patients from Beijing. We identified patients with NVAF undergoing long-term warfarin therapy, and therefore, the patients included in this study had good compliance with their medication. Study indices that included warfarin use and discontinuation rates also are important factors reflecting the quality of warfarin anticoagulation, but these factors were not recorded in this study, but have been previously reported in other studies [32,33].

Conclusions

This study aimed to use data from the Chinese Atrial Fibrillation Registry study to assess the control of anticoagulation therapy in Chinese patients with non-valvular atrial fibrillation (NVAF) treated with warfarin. The study findings showed that the quality of warfarin anticoagulation in Chinese patients with NVAF was generally lower than that recommended in current clinical guidelines. Increased age, a history of bleeding, concomitant drug therapies, and insufficient attention to bleeding risk were associated with reduced time in the therapeutic range (TTR) of the international normalized ratio (INR). A previous history of coronary heart disease (CHD), peripheral arterial disease (PAD), and diabetes mellitus were factors associated with reduced stability of anticoagulation.

Conflict of interest

Dr. Chang-Sheng Ma has received honoraria from Bristol-Myers Squibb (BMS), Pfizer, Johnson & Johnson, Boehringer Ingelheim (BI), and Bayer for giving lectures. Dr. Jian-Zeng Dong also received honoraria from Johnson & Johnson for giving lectures. Dr. Gregory Y.H. Lip is a Consultant for Bayer/Janssen, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseon, and Daiichi-Sankyo, and is a speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo. No fees were directly received personally regarding this study.

Supplement Table 1. Variability of anticoagulation intensity.

Characteristics	SDINR Median (25–75%)	p-Value
Age		
<70y	0.52 (0.37-0.68)	P=0.082
≥70y	0.49 (0.36-0.65)	
Gender		
Male	0.50 (0.36-0.66)	P= 0.607
Female	0.50 (0.37-0.68)	
Stroke/TIA/thromboembolism		
Yes	0.50 (0.36-0.66)	P= 0.740
No	0.50 (0.37-0.67)	
Bleeding history		
Yes	0.50 (0.40-0.67)	P=0.926
No	0.50 (0.36-0.67)	
Bleeding risk score		
<3	0.51 (0.40-0.70)	P=0.099
=3	0.50 (0.35-0.66)	
>3	0.49 (0.37-0.65)	
CHA_2DS_2 – VASc score		
<2	0.49 (0.36-0.66)	P=0.497
≥2	0.51 (0.36-0.67)	
HAS-BLED score		
≤2	0.50 (0.36-0.66)	P=0.087
>2	0.52 (0.38-0.70)	

TIA – transient ischemic attack. The comparison of the SD_{INR} within subgroups defined by HAS-BLED score, CHA_2DS_2-VASc score, bleeding risk score, bleeding or stroke/TIA/thromboembolism history, gender, and age (p>0.05)

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

References:

1. Lip G, Freedman B, De Caterina R, Potpara TS: Stroke prevention in atrial fibrillation: Past, present and future. Comparing the guidelines and practical decision-making. Thromb Haemost, 2017; 117(7): 1230–39
2. Singer DE, Hellkamp AS, Piccini JP et al: Impact of global geographic region on time in therapeutic range on warfarin anticoagulant therapy: Data from the ROCKET AF clinical trial. J Am Heart Assoc, 2013; 2(1): e000067
3. Shen AY, Yao JF, Brar SS et al: Racial/ethnic differences in the risk of intracranial haemorrhage among patients with atrial fibrillation. J Am Coll Cardiol, 2007; 50(4): 309–15
4. Huang CX, Zhang S, Huang DJ et al: Current knowledge and management recommendations of atrial fibrillation 2015. Chin J Cardiac Arrhyth, 2015; 5: 321–84
5. Ogawa S, Koretsune Y, Yasaka M et al: Antithrombotic therapy in atrial fibrillation: Evaluation and positioning of new oral anticoagulant agents. Circ J, 2011; 75(7): 1539–47
6. JCS Joint Working Group: Guidelines for pharmacotherapy of astrial fibrillation (JCS 2013). Circ J, 2014; 78(8): 1997–2021
7. Kirchhof P, Benussi S, Kotecha D et al: 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Europace, 2016; 18(11): 1609–78
8. Lind M, Fahlén M, Kosiborod M et al: Variability of INR and its relationship with mortality, stroke, bleeding and hospitalisations in patients with atrial fibrillation. Thromb Res, 2012; 129(1): 32–35
9. Du X, Ma CS, Wu J et al: Rationale and design of the Chinese Atrial Fibrillation Registry Study. BMC Cardiovasc Disord, 2016; 16: 130
10. Rosendaal FR, Cannegieter SC, van der Meer FJ, Briët E: A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost, 1993; 69(3): 236–39
11. Spertus J, Dorian P, Bubien R et al: Development and validation of the Atrial Fibrillation Effect on QualiTy-of-Life (AFEQT) Questionnaire in patients with atrial fibrillation. Circ Arrhythm Electrophysiol, 2011; 4(1): 15–25
12. Olesen JB, Torp-Pedersen C, Hansen ML, Lip GY: The value of the CHA2DS2-VASc score for refining stroke risk stratification in patients with atrial fibrillation with a CHADS2 score 0-1: A nationwide cohort study. Thromb Haemost, 2012; 107(6): 1172–79
13. Lip GY, Nieuwlaat R, Pisters R et al: Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: The Euro Heart Survey on Atrial Fibrillation. Chest, 2010; 137(2): 263–72
14. January CT, Wann LS, Alpert JS et al: 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. Circulation, 2014; 130(23): 2071–104
15. Pisters R, Lane DA, Nieuwlaat R et al: A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: The Euro Heart Survey. Chest, 2010; 138(5): 1093–100
16. Zulkifly H, Lip GYH, Lane DA: Use of the SAMe-TT2R2 score to predict anticoagulation control in atrial fibrillation and venous thromboembolism patients receiving vitamin K antagonists: A review. Heart Rhythm, 2018; 15(4): 615–23
17. Palomäki A, Mustonen P, Hartikainen JE et al: Underuse of anticoagulation in stroke patients with atrial fibrillation – the FibStroke Study. Eur J Neurol, 2016; 23(1): 133–39
18. Doğan V, Başaran Ö, Beton O et al: Gender-related differences in presentation and treatment of patients with non-valvular atrial fibrillation: Results from RAMSES study. Turk Kardiyol Dem Ars, 2017; 45(1): 16–25
19. Shewale A, Johnson J, Li C et al: Variation in anticoagulant recommendations by the guidelines and decision tools among patients with atrial fibrillation. Healthcare, 2015; 3(1): 130–45
20. Chiang CE, Wang KL, Lip GY: Stroke prevention in atrial fibrillation: An Asian perspective. Thromb Haemost, 2014; 111(5): 789–97
21. Shen AY, Chen W, Yao JF et al: Effect of race/ethnicity on the efficacy of warfarin: Potential implications for prevention of stroke in patients with atrial fibrillation. CNS Drugs, 2008; 22(10): 815–25
22. Amin A, Deitelzweig S, Jing Y et al: Estimation of the impact of warfarin's time-in-therapeutic range on stroke and major bleeding rates and its influence on the medical cost avoidance associated with novel oral anticoagulant use-learnings from ARISTOTLE, ROCKET-AF, and RE-LY trials. J Thromb Thrombolysis, 2014; 38(2): 150–59
23. Kaatz S: Determinants and measures of quality in oral anticoagulation therapy. J Thromb Thrombolysis, 2008; 25(1): 61–66
24. Vanerio G: international normalized ratio variability: A measure of anticoagulation quality or a powerful mortality predictor. J Stroke Cerebrovasc Dis, 2015; 24(10): 2223–28
25. Razouki Z, Ozonoff A, Zhao S et al: Improving quality measurement for anticoagulation: Adding international normalized ratio variability to percent time in therapeutic range. Circ Cardiovasc Qual Outcomes, 2014; 7(5): 664–69
26. Pastori D, Pignatelli P, Menichelli D et al: Integrated care management of patients with atrial fibrillation and risk of cardiovascular events: The ABC (Atrial fibrillation Better Care) pathway in the ATHERO-AF study cohort. Mayo Clin Proc, 2018 [Epub ahead of print]
27. Proietti M, Romiti GF, Olshansky B et al: Improved outcomes by integrated care of anticoagulated patients with atrial fibrillation using the simple ABC (Atrial Fibrillation Better Care) pathway. Am J Med, 2018; 131(11): 1359–66
28. Lip GYH. The ABC pathway: An integrated approach to improve AF management. Nat Rev Cardiol, 2017; 14(11): 627–28
29. Apostolakis S, Sullivan RM, Olshansky B, Lip GYH: Factors affecting quality of anticoagulation control among patients with atrial fibrillation on warfarin: The SAMe-TT_2R_2 score. Chest, 2013; 144(5): 1555–63
30. Pritchett RV, Bem D, Turner GM et al: Improving the prescription of oral anticoagulants in atrial fibrillation: A systematic review. Thromb Haemost, 2019; 119(2): 294–307
31. Raparelli V, Proietti M, Cangemi R et al: Adherence to oral anticoagulant therapy in patients with atrial fibrillation. Focus on non-vitamin K antagonist oral anticoagulants. Thromb Haemost, 2017; 117(2): 209–18
32. Chang SS, Dong JZ, Ma CS et al: Current status and time trends of oral anticoagulation use among Chinese patients with nonvalvular atrial fibrillation: The Chinese atrial fibrillation registry study. Stroke, 2016; 47(7): 1803–10
33. Wang ZZ, Du X, Wang W et al: Long-term persistence of newly initiated warfarin therapy in Chinese patients with nonvalvular atrial fibrillation. Circ Cardiovasc Qual Outcomes, 2016; 9(4): 380–87

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]