Use of Warfarin at Discharge Among Acute Ischemic Stroke Patients With Nonvalvular Atrial Fibrillation in China

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Background and Purpose—Guidelines recommend oral anticoagulation for ischemic stroke patients with atrial fibrillation, and previous studies have shown the underuse of anticoagulation for these patients in China. We sought to explore the underlying reasons and factors that currently affect the use of warfarin in China.

Methods—From June 2012 to January 2013, 19,604 patients with acute ischemic stroke were admitted to 219 urban hospitals voluntarily participating in the China National Stroke Registry II. Multivariable logistic regression models using the generalized estimating equation method were used to identify patient/hospital factors independently associated with warfarin use at discharge.

Results—Among the 952 acute ischemic stroke patients with nonvalvular atrial fibrillation, 19.4% were discharged on warfarin. The risk of bleeding (52.8%) and patient refusal (31.9%) were the main reasons for not prescribing anticoagulation. Larger/teaching hospitals were more likely to prescribe warfarin. Older patients, heavy drinkers, patients with higher National Institutes of Health Stroke Scale score on admission were less likely to be given warfarin, whereas patients with history of heart failure and an international normalized ratio between 2.0 and 3.0 during hospitalization were significantly associated with warfarin use at discharge.

Conclusions—The rate of warfarin use remains low among patients with ischemic stroke and known nonvalvular atrial fibrillation in China. Hospital size and academic status together with patient age, heart failure, heavy alcohol drinking, international normalized ratio in hospital, and stroke severity on admission were each independently associated with the use of warfarin at discharge. There is much room for improvement for secondary stroke prevention in nonvalvular atrial fibrillation patients in China. (Stroke. 2016;47:464-470. DOI: 10.1161/STROKEAHA.115.011833.)

Key Words: atrial fibrillation • China • secondary prevention • stroke • warfarin

Atrial fibrillation (AF) is a poten risk factor for ischemic stroke.1 Oral anticoagulants (OACs) including warfarin and new non–vitamin K OACs have shown great efficacy for the prevention of stroke and embolism in patients with AF2–5 and are recommended for secondary prevention by major guidelines.6 However, several studies have shown the underuse of oral anticoagulation therapy for real-world AF patients.7 This phenomenon is especially prevalent in China according to previous studies.8–10 Recent compelling evidence demonstrates that anticoagulation offers important benefits to East Asian patients with AF.11 Although efforts have been made to improve the quality of care for stroke patients in China,12 whether the underuse of warfarin has improved and the underlying reasons for underuse have not been previously defined. This study aims to investigate the use of warfarin in ischemic stroke patients with nonvalvular AF (NVAF) at discharge and to explore the factors with underuse at the hospital, physician, and patient level.

Methods

China National Stroke Registry II Design and Site Selection

China National Stroke Registry II (CNSR II), launched in 2012 by the Ministry of Health of China, is the nationwide initiative in China to establish a reliable national stroke database for evaluating the delivery of stroke care in clinical practice and to identify areas that need further improvement when compared with CNSR I in 2007.13 The criteria for site selection in China National Stroke Registry I (CNSR I) has been published13 and in order for the hospital characteristics to be similar
between CNSR I and CNSR II, the same criteria was used for selection. Among the 219 hospitals participating in CNSR II, 29 hospitals were excluded because they did not enroll eligible patients or record warfarin use at discharge. The study was approved by the central Institutional Review Board at Beijing Tiantan Hospital. Every participant provided signed informed consent before his/her participation.

Case Enrollment and Target Population
Patients were recruited consecutively from all 219 hospitals from June 2012 to January 2013 if they met the following criteria: (1) age>18 years; (2) diagnosis within 7 days of the index event of ischemic stroke, transient ischemic attack, spontaneous intracerebral hemorrhage, or subarachnoid hemorrhage; (3) direct hospital admission from a physician’s clinic or emergency department; and (4) informed consent provided by patient or legally authorized representative.

Data Collection and Management
Trained research coordinators at each hospital reviewed the medical records daily to identify, obtain informed consent, and enroll consecutive patients. The data abstracted from medical records include patient demographics, health insurance status, education level, vascular risk factors, medications, selected laboratory tests, and discharge status. Hospital-level characteristics including geographic region, teaching status, number of beds, and annual stroke discharges were also collected. According to annual report on health statistics of China,14 hospitals were divided into 3 regions: Eastern, Central, and Western. Academic status was defined as a hospital affiliated with a specific university. Hospital bed size was the number of total inpatient beds per site. Annual stroke discharge was the number of discharged patients diagnosed with stroke per year per hospital.

Eligibility and Criteria
The NVAF patients were defined as patients with AF who were diagnosed at discharge by researchers according to the 12-lead ECG/24-hour Holter cardiac rhythm recording at the time of admission or during the hospitalization, and without mitral or aortic valve disease. Acute ischemic stroke was diagnosed according to World Health Organization criteria15 combined with brain computed tomography or magnetic resonance confirmation. Patients with an identified contraindication to anticoagulation and patients who were dead at discharge were excluded. The OACs included in our study were warfarin and oral factor Xa inhibitors. However, because only 4 patients took factor Xa inhibitors at discharge, they were excluded from the analysis. The rate of warfarin use at discharge was defined as the total number of acute ischemic stroke patients with NVAF receiving warfarin at discharge divided by the total number of eligible patients without identified contraindication to anticoagulation.

Stroke risk was calculated at discharge using the CHADS score (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and previous stroke or transient ischemic attack)19 and CHA₂DS₂-VASc score (congestive heart failure, hypertension, age 65–74 years and age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack; vascular disease, and sex category [female]). The lowest CHADS, and CHA₂DS₂-VASc scores at discharge were 2 because all the patients had history of ischemic stroke. Abnormal liver function and renal function were defined as aspartate transaminase/alanine aminotransferase/alkaline phosphatase >3× upper limit normal and serum creatinine ≥220 μmol/L, respectively, according to the criteria associated with the HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol concomitantly) score.18

Reasons Why Anticoagulation Was Not Administered at Discharge
The reasons for not prescribing anticoagulation to patients with NVAF were prospectively recorded based on those proposed by the Get With The Guidelines-Stroke project in the United States.19 For patients without any contraindication, we analyzed the reasons why anticoagulation were not administered at the physician level. Barriers to physician adherence to practice guidelines were organized into groups as described in previous study.20 The barriers were categorized into physician knowledge (lack of awareness or lack of familiarity), attitudes (lack of agreement, lack of self-efficacy, lack of outcome expectancy, or the inertia of previous practice), or behavior (external barriers including patient/guideline/environmental factors).

Statistical Analysis
Continuous variables are reported as mean±SD or median with interquartile ranges, and categorical variables are reported as percentages. Baseline hospital-level and patient-level characteristics were compared between patients with and without warfarin use at discharge by using Pearson χ² tests for categorical variables and Mann–Whitney U test for continuous variables. The multivariable logistic regression model with the generalized estimating equation method (that accounts for in-hospital clustering) was used to identify patient and hospital characteristics independently associated with warfarin use. In the model, we adjusted for factors that were significant in the univariate analysis (P<0.05). All tests are 2 tailed with P<0.05 to be considered as the level of statistical significance. All analyses were performed by using SAS version 9.3 software (SAS Institute, Cary, NC).

Results
From a total of 25018 patients with acute cerebrovascular events in the registry of which 19604 (78.4%) were diagnosed with acute ischemic stroke on admission and among these 1198 had NVAF. We excluded 182 NVAF patients with contraindications to anticoagulation and 64 who died during hospitalization. Therefore, 952 patients with known NVAF and without contraindication to anticoagulation were included in this study (Figure). Among these patients, 19.4% received warfarin at discharge (including 3.8% given both warfarin and an antiplatelet agent), 59.9% were on an antiplatelet agent alone, and 20.7% were on neither warfarin nor an antiplatelet agent.

Reasons Why Anticoagulation Drugs Were Not Administered at Discharge
Among 182 patients with ≥1 anticoagulation contraindications, the identified reasons included the risk for bleeding (52.8%), patient/family refusal (31.9%), terminal illness (9.9%), allergy to or complication related to warfarin or heparins (history or current; 5.0%), serious adverse effect to medication (2.8%), and unacceptable high risk of falling (1.1%). For patients without any anticoagulation contraindication, the underlying reasons for withholding anticoagulation were not available for 190 NVAF patients. Among the remaining 577 patients, the most common reasons why anticoagulation was not administered at the physician level were factors that affected physician behavior such as external barriers (54.1%) including failure in coordination of regular international normalized ratio (INR) testing (48.7%), lack of reimbursement (3.0%), and lack of access to warfarin (2.4%). Factors that affected physician knowledge were lack of familiarity (0.5%) and lack of awareness (0.5%). Additional factors that affected physician attitudes included lack of outcome expectancy (0.4%) and unspecified factors (54.3%). Some physicians had >1 reason, hence the total percentage exceeds 100%.
Hospital- and Patient-Level Determinants of Warfarin Use

By univariable analysis, eligible patients from 85 (44.7%) of 190 hospitals were discharged on warfarin. Warfarin use was more frequent at hospitals with larger numbers of beds ($P=0.01$) and larger annual volumes of stroke discharges ($P=0.049$). In addition, patients discharged on warfarin were more likely to be treated at academic hospitals (68.2%) than those treated at nonacademic hospitals (31.8%; $P=0.004$; Table 1).

Patients treated with warfarin at discharge were younger ($P<0.0001$), more likely to have a history of heart failure ($P=0.003$), and INR in the range of 2.0 to 3.0 during hospitalization ($P=0.003$). In contrast, heavy alcohol drinkers ($P=0.006$) and patients with a history of hypertension ($P=0.02$) or higher National Institutes of Health Stroke Scale scores on admission ($P=0.0007$) were less likely to receive anticoagulants than those without these conditions. Considering the CHADS$_2$ score, patients with higher scores (≥3) were less likely to receive anticoagulants ($P<0.0001$; Table 2).

By multivariate analysis, patients treated in larger and teaching hospitals were associated with an increased odds of being treated with warfarin at discharge (odds ratio [OR], 1.0004; 95% confidence interval [CI], 1.0001–1.0007 and OR, 1.54; 95% CI, 1.02–2.33, respectively; Table 3).

Multivariate analysis also revealed that younger age (OR, 0.97; 95% CI, 0.95–0.99) and lower National Institutes of

Table 1. Characteristics of Hospitals Where Eligible Patients Were and Were Not Discharged With Warfarin

<table>
<thead>
<tr>
<th>Variable, Level</th>
<th>All CNSR II Hospitals</th>
<th>With Warfarin</th>
<th>Without Warfarin</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of hospitals, n</td>
<td>190</td>
<td>85</td>
<td>105</td>
<td>…</td>
</tr>
<tr>
<td>Hospital beds, median (IQR)</td>
<td>1000 (600–1650)</td>
<td>1200 (780–1900)</td>
<td>900 (526–1400)</td>
<td>0.01</td>
</tr>
<tr>
<td>Annual stroke discharges, median (IQR)</td>
<td>437 (299–723)</td>
<td>478 (325–781)</td>
<td>417 (264–672)</td>
<td>0.049</td>
</tr>
<tr>
<td>Geographic region, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.97</td>
</tr>
<tr>
<td>East</td>
<td>126 (57.5)</td>
<td>52 (61.2)</td>
<td>60 (57.1)</td>
<td></td>
</tr>
<tr>
<td>Middle</td>
<td>51 (23.3)</td>
<td>12 (14.1)</td>
<td>28 (26.7)</td>
<td></td>
</tr>
<tr>
<td>West</td>
<td>42 (19.2)</td>
<td>21 (24.7)</td>
<td>17 (16.2)</td>
<td></td>
</tr>
<tr>
<td>Hospital type, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.004</td>
</tr>
<tr>
<td>Nonteaching</td>
<td>92 (42)</td>
<td>27 (31.8)</td>
<td>55 (52.4)</td>
<td></td>
</tr>
<tr>
<td>Teaching</td>
<td>127 (58)</td>
<td>58 (68.2)</td>
<td>50 (47.6)</td>
<td></td>
</tr>
</tbody>
</table>

CNSR II indicates China National Stroke Registry II; and IQR, interquartile range.
Health Stroke Scale score on admission (OR, 0.95; 95% CI, 0.93–0.98) were independently associated with warfarin use. Patients with heart failure (OR, 3.03; 95% CI, 1.62–5.69) and INR in the range of 2 to 3 during hospitalization (OR, 7.32; 95% CI, 2.24–23.86) were also more likely to be discharged on warfarin. However, patients who were heavy alcohol drinkers were less likely to receive warfarin (OR, 0.58; 95% CI, 0.34–0.99; Table 3).

Discussion
This study demonstrates that the rate of warfarin use among acute ischemic stroke patients with NVAF in China remains unacceptably low. The main identified reasons for not prescribing anticoagulation were the perceived risk of bleeding and patient refusal. The main barrier affecting physician behavior was the lack of access to coordinated regular INR testing. Larger/teaching hospitals were more likely to...
prescribe warfarin. Older patients, heavy alcohol drinkers, and patients with higher National Institutes of Health Stroke Scale score on admission were independently associated with less frequent use of warfarin, whereas patients with history of heart failure and an INR between 2.0 and 3.0 during hospitalization were significantly associated with warfarin use at discharge.

When compared with the previous studies from China that launched before 2010\textsuperscript{8,21} (in which anticoagulants use in hospitalized AF patients were 11\% and 14.2\%, respectively), the rate of warfarin use was not increased substantially. In contrast, anticoagulation use among eligible AF patients improved from 88.4\% to 95.2\% during 7 years in the Get With The Guidelines-Stroke in the United States\textsuperscript{19}.

Given that the substantial underestimate of warfarin in China, we explored the reasons why anticoagulants were not administered at the patient, physician, and hospital levels. Among documented reasons, the perceived risk for bleeding and patient/family refusal were the main concerns. In addition, for patients without any identified contraindication to anticoagulation, the most important factor affecting the physician guideline adherence was lack of access to coordinated regular INR test other than physician knowledge and attitude. In comparison with other studies\textsuperscript{19,22} the problems of patient refusal and failure in regular INR tests were particularly salient in China.

The possible explanations may be as follows: first, owing to the narrow therapeutic window and drug or food interactions of warfarin, patients require frequent INR testing and dose adjustments that decrease the appeal of using warfarin. Second, inadequate comprehensive community health services\textsuperscript{23} and availability of self-monitoring device technologies make frequent INR testing difficult in China. Importantly, the new non–vitamin K OACs (eg, dabigatran, rivaroxaban, and apixaban) are attractive alternatives to warfarin because they do not require monitoring the INR and are associated with a sharply reduced risk of intracranial hemorrhage.\textsuperscript{8,24,25} However, their higher price and lack of coverage by the public health insurance in China are currently major barriers to their widespread use.

Consistent with results from other recent studies\textsuperscript{8,19,26} we also found that younger age was a determinant of warfarin use. The underlying reason may be the concerns of high bleeding rates in older patients. However, because stroke risk increases with age in NVAF, the absolute benefit of OACs increases as patients grow older.\textsuperscript{27} Hence, it is important for clinicians to recognize that patient age itself should not be a reason to avoid using OACs as preventive therapy in patients with NVAF.

In addition, the history of heart failure was associated with higher frequency of warfarin treatment. The possible explanation may be that congestive heart failure has been demonstrated to strongly be associated with increased thromboembolism and mortality and independently add to the risk prediction of stroke.\textsuperscript{28}

Our finding that heavy alcohol drinking was independently associated with avoiding warfarin use is supported by the HAS-BLED score that has been recommended by guidelines\textsuperscript{29,30} to identify patients with increased risk of bleeding. Furthermore, higher National Institutes of Health Stroke Scale score on admission was another independent factor associated with reduced warfarin use. More severe condition may be related to larger size of infarction that raise physician concerns about prescribing warfarin because of the potentially heightened risk of symptomatic hemorrhagic transformation.

At hospital level, larger and teaching hospitals were associated with the use of warfarin for eligible patients at discharge. Our finding of increased prescription of warfarin potentially related to institutional experience is consistent with the results in the Get With The Guidelines-Stroke Registry.\textsuperscript{19} Previous study\textsuperscript{11} has shown that hospitals with more beds tend to have more specialized services and greater physician and staff expertise. Thus, hospitals with greater experience and focus on the care of stroke patients seem to be associated with a greater adherence to anticoagulation guidelines.

There are limitations of our study. First, participation by hospitals was voluntary and thus potentially self-selected to focus on high standard of stroke care. Therefore, results from these hospitals may not reflect the true magnitude of warfarin underuse nationwide in China. Second, our data were confined to inpatient care and discharge prescription of warfarin. Time in therapeutic range of warfarin, and postdischarge patient adherence, could not be assessed. Finally, the number of AF patients may be underestimated in our study because of under-detection of AF. The appropriate use of warfarin among acute ischemic stroke patients with AF in China may consequently

Table 3. Multivariate Analyses of Hospital and Patient Characteristics Associated With Prescription of Anticoagulation in Eligible Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 1-y increase)</td>
<td>0.97</td>
<td>0.95–0.99</td>
<td>0.001</td>
</tr>
<tr>
<td>Previous history of heart failure</td>
<td>3.03</td>
<td>1.62–5.69</td>
<td>0.0006</td>
</tr>
<tr>
<td>Heavy drinker</td>
<td>0.58</td>
<td>0.34–0.99</td>
<td>0.045</td>
</tr>
<tr>
<td>INR (2–3) during hospitalization</td>
<td>7.32</td>
<td>2.24–23.86</td>
<td>0.001</td>
</tr>
<tr>
<td>NIHSS on admission</td>
<td>0.95</td>
<td>0.93–0.98</td>
<td>0.002</td>
</tr>
<tr>
<td>Hospital beds (per 1-bed increase)</td>
<td>1.0004</td>
<td>1.0001–1.0007</td>
<td>0.003</td>
</tr>
<tr>
<td>Teaching hospitals</td>
<td>1.54</td>
<td>1.02–2.33</td>
<td>0.041</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; INR, international normalized ratio; NIHSS, the National Institutes of Health Stroke Scale; and OR, odds ratio.
be even lower than what we report here. Prolonged cardiac monitoring to detect covert paroxysmal AF in patients with ischemic stroke or transient ischemic attack is crucial to optimize appropriate anticoagulation in the future.

In conclusion, the use of warfarin in stroke patients with NVAF in China has not improved substantially in recent years. Concerns about bleeding during anticoagulation and access to coordination INR monitoring are the main obstacles. Efforts to strengthen knowledge about the overall benefit of warfarin for most NVAF patients, to promote use of the new OACs, to improve the primary healthcare delivery to facilitate INR monitoring, and to increase the quality of stroke care in small and nonacademic hospitals will be important to optimize the use of anticoagulants among NVAF patients in China.

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Disclosures
None.

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