Ischemic Stroke and Intracranial Hemorrhage With Aspirin, Dabigatran, and Warfarin
Impact of Quality of Anticoagulation Control

Chi-Wai Ho, MBBS⁎; Mei-Han Ho, MBBS⁎; Pak-Hei Chan, MBBS; Jo-Jo Hai, MBBS; Emmanuel Cheung, MBBS; Chun-Yip Yeung, MBBS; Kui-Kai Lau, MBBS; Koon-Ho Chan, MD; Chu-Pak Lau, MD; Gregory Y.H. Lip, MD; Gilberto Ka-Kit Leung, MS; Hung-Fat Tse, MD, PhD; Chung-Wah Siu, MD

Background and Purpose—Little is known about the impact of quality of anticoagulation control, as reflected by time in therapeutic range (TTR), on the effectiveness and safety of warfarin therapy in Chinese patients with atrial fibrillation. We investigated the risks of ischemic stroke and intracranial hemorrhage (ICH) in relation to warfarin at various TTRs in a real-world cohort of Chinese patients with atrial fibrillation receiving warfarin compared with those on dabigatran, aspirin, and no therapy.

Methods—This is an observational study.

Results—Of 8754 Chinese patients with atrial fibrillation and CHA2DS2-VASc ≥1 (79.5±9.2 years; CHA2DS2-VASc, 4.1±1.5; and Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile International Normalized Ratio, Elderly (>65 years), Drugs/Alcohol Concomitantly [HAS-BLED], 2.2±0.9), 16.3% received warfarin, 41.1% aspirin, 4.5% dabigatran, and 38.1% received no therapy. The incidence of ischemic stroke was highest in patients with no therapy (10.38%/y), followed by patients on aspirin (7.95%/y). The incidence of stroke decreased progressively with increasing TTR quartiles (<17.9%, 17.9~38.8%, 38.8~56.2%, and >56.2%) from 7.34%/y (first quartile) to 3.10%/y (fourth quartile). Patients on dabigatran had the lowest incidence of stroke among all groups (2.24%/y). The incidence of ICH was lowest in patients on dabigatran (0.32%/y) compared with those on warfarin (0.90%/y), aspirin (0.80%/y), and no therapy (0.53%/y). ICH incidence decreased with increasing TTR from 1.37%/y (first quartile) to 0.74%/y (fourth quartile).

Conclusions—In Chinese patients with atrial fibrillation, the benefits of warfarin therapy for stroke prevention and ICH risk are closely dependent on the quality of anticoagulation, as reflected by TTR. Even at the top TTR quartile, warfarin was associated with a higher stroke and ICH risk than dabigatran. (Stroke. 2015;46:23-30. DOI: 10.1161/STROKEAHA.114.006476.)

Key Words: atrial fibrillation, intracranial hemorrhages

See related article, p 5.

Atrial fibrillation (AF) confers a 5-fold higher risk of ischemic stroke and accounts for >20% of all ischemic strokes.1 Although warfarin therapy with a target international normalized ratio (INR) between 2.0 and 3.0 has been shown effective in reducing ischemic stroke and mortality among patients with nonvalvular AF,2,4 its benefit could be offset by the increased intracranial hemorrhage (ICH) inherent with the therapy. This is of particular relevance to Asian populations such as the Chinese given a higher baseline risk of ICH among Chinese,5-7 thus undermining the potential benefit of any antithrombotic therapy. This fear may be reflected in the gross underutilization of warfarin therapy (15%~20%) and the high prevalence of aspirin therapy (as a perceived alternative to warfarin) in these populations.8,9,10 Even among those on warfarin therapy, the quality of anticoagulation has been poor in Chinese (and other Asian) patients even in the setting of randomized clinical trials.11,12 The time in therapeutic range (TTR), reflecting the proportion of time spent within therapeutic range of 2.0 to 3.0, has emerged as a marker reflecting the quality of anticoagulation control while on warfarin therapy. The TTR has been shown to be closely correlated with ischemic stroke, hemorrhage, and mortality.13-15

Received June 16, 2014; final revision received September 11, 2014; accepted September 15, 2014.
From the Cardiology Division (C.-W.H., M.-H.H., P.-H.C., J.-J.H., E.C., C.-P.L., H.-F.T., C.-W.S.), Endocrinology Division (C.-Y.Y.), and Neurology Division (K.-K.L., K.-H.C.), Department of Medicine, Queen Mary Hospital and Division of Neurosurgery, Department of Surgery, Li Ka Shing Faculty of Medicine (G.K.-K.L.), University of Hong Kong, Hong Kong SAR, China; and University of Birmingham Centre for Cardiovascular Sciences, City Hospital, University Department of Medicine, Birmingham, United Kingdom (G.Y.H.L.).
*C.-W. Ho and M.-H. Ho contributed equally.
The online-only Data Supplement is available with this article at http://stroke.ahajournals.orglookup/suppl/doi:10.1161/STROKEAHA.114.006476/-/DC1.
Correspondence to Chung-Wah Siu, MD, Cardiology Division, Department of Medicine, The University of Hong Kong, Hong Kong, China. E-mail cwsiu@hku.hk
© 2014 American Heart Association, Inc.
Stroke is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.114.006476
Nonetheless, data on the impact of TTR of warfarin therapy on the risk of ischemic stroke or ICH in Chinese patients are limited. The non–vitamin K oral anticoagulants (NOACs, previously referred to as new or novel oral anticoagulants, eg, dabigatran, rivaroxaban, and apixaban) have been shown in randomized trials to have relative efficacy, safety, and convenience compared with warfarin in patients with AF. Thus, international guidelines recommend the NOACs in preference to conventional warfarin therapy for stroke prevention where possible. However, there are limited published real-world data in Chinese AF populations comparing the efficacy and safety of dabigatran, warfarin therapy at different TTRs, and aspirin therapy.

In this analysis, we aimed to investigate the risk of ischemic stroke and ICH in relation to TTR in a real-world cohort of Chinese patients with AF receiving warfarin (at different degrees of anticoagulation control, as reflected by TTR) and compared outcomes with those on dabigatran, aspirin, and no therapy.

Methods

Study Design
This was an observational study based on a hospital-based AF registry. The study protocol was approved by the local institutional review board. Informed consents were not obtained from the patients given the registry nature of the study; however, all patient records or information was anonymized and deidentified before analysis. Patients diagnosed to have AF in Queen Mary Hospital, Hong Kong, from July 1997 to December 2011, were identified via the computerized database of clinical management system. Patients were excluded if they had significant valvular heart disease and previous valvular replacement or had incomplete clinical and follow-up data. In addition, patients with AF diagnosed after the commercial availability of dabigatran were also identified (Figure I in the online-only Data Supplement). All hospital admissions, outpatient clinic visits, laboratory results, and radiological images have been recorded in the computer-based clinical management system since 1996. Demographic data, cardiovascular risk factors, and medications were recorded at baseline. The index date was defined as the date of the first occurrence of AF. For registration of outcomes during follow-up, a blanking period of 14 days after the index date was applied as the occurrence of a stroke or ICH within the first few days of diagnosis of AF is most likely related to initial presentation rather than a new event. Stroke risk was calculated at baseline using the Rosendaal method, in which INR was quantified as 0 in every patient as none of patients were on warfarin therapy at baseline. Subsequent occurrence of risk factor contributory to CHA2DS2-VASc score had not been taken into account. The Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile International Normalized Ratio, Elderly (>65 years), Drugs/Alcohol Comorbidities score was likewise calculated at baseline as a measure of bleeding risk. Uncontrolled hypertension was defined as systolic blood pressure >160 mm Hg at baseline and subsequent visit-to-visit changes in systolic blood pressure had not been taken in account. Similarly, liver disease as determined by the derangement in liver biochemical and renal disease as determined by serum creatinine level were only assessed at baseline, subsequent changes had not been taken into account. The labile INR criterion was quantified as 0 in every patient as none of patients were on warfarin at baseline.

The final analysis included 8754 patients with nonvalvular AF with CHA2DS2-VASc ≥1, who were classified according to their antithrombotic strategies: warfarin, aspirin, and no antithrombotic therapy. Among patients receiving warfarin therapy, TTR was calculated for each patient using Rosendaal method, in which INR was assumed to change in a linear manner between measurements, and INR values on the days with no measurement were interpolated. The percentage of time during which a patient had an INR within 2.0 to 3.0 was taken as TTR. Patients were then further classified into 4 groups according to quartiles of TTR.

Outcomes, Variables, and Data Source
The primary outcome was hospital admission for ischemic stroke, whereas the secondary outcome was admission for ICH. Stroke was defined as a neurological deficit of sudden onset, persisting for >24 hours, corresponding to a vascular territory and not explained by other causes (eg, trauma, infection). ICH comprises intracerebral hemorrhage, subarachnoid hemorrhage, and subdural hemorrhage. Neuroimaging evidence, either from computed tomography or MRI, was required to confirm the diagnosis of stroke and ICH. Data were retrieved from the medical records and discharge summaries from the territory-wide information network of all public hospitals in Hong Kong.

Statistical Analysis
Continuous and discrete variables are expressed as mean±SD and percentages, respectively. Statistical comparison of the baseline clinical characteristics was performed using Student t test or 1-way ANOVA as appropriate. Kaplan–Meier survival analyses with the log-rank test were performed and Cox proportional hazards regression model was used to calculate hazard ratios (HRs) of some predictive factors and their 95% confidence interval (CIs) for the incidence of stroke. Calculations were performed using SPSS software (version 12.0). All tests were 2-sided, and P values were considered significant if <0.05.

Results
A total of 8754 Chinese patients (79.5±9.2 years; women, 56.7%) with nonvalvular AF and CHA2DS2-VASc score ≥1 was included in the final analysis. Table 1 summarizes the clinical characteristics of the study population. The mean CHA2DS2-VASc and HAS-BLED scores were 4.1±1.5 and 2.2±0.9, respectively.

Of this cohort, 1428 patients (16.3%) were on warfarin. The quartiles of individual TTR were categorized as follows: <17.9% (first quartile), 17.9% to 38.8% (second quartile), 38.8% to 56.2% (third quartile), and >56.2% (fourth quartile). Increasing age, diabetes mellitus, renal failure on dialysis, and higher CHA2DS2-VASc score were associated with low TTRs (ie, TTRs in the first quartile; Table 1). In multivariate analysis, only increasing age (HR, 1.03; 95% CI, 1.01–1.04), diabetes mellitus (HR, 1.40; 95% CI, 1.07–1.82), and renal failure on dialysis (HR, 2.63; 95% CI, 1.24–5.60) were independent predictors of poor TTR.

In addition, 3600 patients (41.1%) were on aspirin (80–160 mg daily), 393 patients (4.5%) were on dabigatran, and 3333 patients (38.1%) received neither warfarin nor aspirin (no antithrombotic therapy).

Ischemic Stroke
After a mean follow-up of 3.0±3.2 years (2610 patient-years), there were 2005 patients who developed an ischemic stroke (23.8%) with an annual incidence of ischemic stroke of 7.74%/y. Table 2 summarizes factors predictive of ischemic stroke together with the corresponding HRs based on Cox proportional hazard model and 95% CIs. On univariate analysis, increasing age, female sex, hypertension, diabetes mellitus, prior ischemic stroke, smoking history, and renal failure on dialysis were associated with the increasing risk of ischemic stroke, as was type of antithrombotic strategies.

Downloaded from http://stroke.ahajournals.org/ by guest on July 24, 2017
As expected, patients received no therapy had the highest incidence of ischemic stroke (10.38%/y), followed by those on aspirin (7.95%/y; Figure 1). Among patients receiving warfarin, the annual incidence of ischemic stroke decreased progressively with increasing TTRs, from 7.34%/y in the first quartile, 5.95%/y in the second quartile, and 4.39%/y in the third quartile to 3.10%/y in the fourth quartile. The annual incidence of ischemic stroke was the lowest among those taking dabigatran (2.24%/y; Figure 1). Figure 2 shows a Kaplan–Meier analysis of ischemic stroke among patients on dabigatran, warfarin at different quartiles of TTR, aspirin, and no therapy (log-rank, 199; P<0.0001).

On multivariate analysis, increasing age (age, 65–75 years: HR, 1.56; 95% CI, 1.22–2.00 and age, ≥75 years: HR, 1.82; 95% CI, 1.43–2.31), female sex (HR, 1.16; 95% CI, 1.05–1.29), hypertension (HR, 1.27; 95% CI, 1.14–1.40), diabetes mellitus (HR, 1.27; 95% CI, 1.14–1.40), prior ischemic stroke (HR, 1.27; 95% CI, 1.14–1.40), and renal failure on dialysis (HR, 1.43; 95% CI, 1.06–1.93) were associated with the increasing risk of ischemic stroke (Table 2). Importantly, the use of aspirin, warfarin, and dabigatran were all associated with lower risk of ischemic stroke. For those on warfarin, specifically, increasing TTR was associated with lower incidence of ischemic stroke (first quartile: adjusted HR, 0.71; 95% CI, 0.58–0.87; second quartile: HR, 0.56; 95% CI, 0.45–0.69; third quartile: HR, 0.42; 95% CI, 0.33–0.53; and fourth quartile: HR, 0.31; 95% CI, 0.23–0.40).

Patients on aspirin had a comparable HR with those patients on warfarin at the lowest quartile (HR, 0.73; 95% CI, 0.67–0.81 versus HR, 0.71; 95% CI, 0.58–0.87; Table 2). Despite the decreasing risk of ischemic stroke with increasing TTR in patients on warfarin, patients on dabigatran had
the lowest ischemic stroke risk (HR, 0.20; 95% CI, 0.12–0.34) among all antithrombotic strategies. Further analysis comparing patients on warfarin with TTR ≥70% (n=154) and patients on dabigatran, despite comparable CHA2DS2-VASc (4.10±1.53 versus 4.12±1.49; P=0.90) and age (73.8±9.2 versus 74.5±9.5 years; P=0.48), the risk of ischemic stroke in patients on dabigatran remained lower than of patients on warfarin with TTR ≥70% (HR, 0.31; 95% CI, 0.15–0.66; Figure II in the online-only Data Supplement). The annual ischemic stroke for patients on warfarin with TTR ≥70% remained higher than those on dabigatran (3.69%/y versus 2.24%/y).

As the registry including patients diagnosed AF during a long period of time, during which awareness and guidelines for treatment had changed, separate analyses of patients diagnosed AF before and after 2008 were thus performed. Although the overall trends were qualitatively comparable, patients with AF diagnosed before 2008 had higher incidences of ischemic stroke (as well as ICH) in all treatment groups (Figures III and IV in the online-only Data Supplement). As a result, the difference in annual incidence of ischemic stroke between those on warfarin at the top quartile and those on dabigatran narrowed.

**Intracranial Hemorrhage**

There were 195 ICHs during the study period (0.75%/y): 121 intracerebral hemorrhages (62.1%), 52 subdural hemorrhages (26.7%), and 22 subarachnoid hemorrhages (11.2%). The factors predictive of ICH based on Cox proportional hazard models were as follows: age >75 years (adjusted HR, 2.93; 95% CI, 1.28–6.68), prior ICH (HR, 2.49; 95% CI, 1.30–4.77), hypertension (HR, 1.42; 95% CI, 1.04–1.93), and diabetes mellitus (1.55; 95% CI, 1.12–2.12; Table 3). Also, warfarin therapy with the TTR in the lowest quartile
was associated with increased risk of ICH (HR, 2.40; 95% CI, 1.39–4.14).

The annual incidence of ICH varied according to the types of antithrombotic strategies (Figure 3). Among patients on warfarin, the incidence of ICH decreased with increasing quartiles of TTR. The incidences of ICH among patients on warfarin from the second quartile to the fourth quartile (0.74%/y–0.86%/y) were comparable with that on aspirin (0.80%/y). Patients on dabigatran had the lowest incidence of ICH (0.32%/y), which was lower than that of patients with no therapy (Figure 3). Furthermore, after excluding patients with prior ICH (because of the difference in proportion of patients with history of prior ICH among various treatment groups), the

### Table 3. Associations Between Baseline Factors and Intracranial Hemorrhage

<table>
<thead>
<tr>
<th></th>
<th>No. of Intracranial Hemorrhage</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HR (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>6</td>
<td>Reference</td>
<td>...</td>
</tr>
<tr>
<td>65–75</td>
<td>54</td>
<td>1.90 (0.82–4.42)</td>
<td>0.137</td>
</tr>
<tr>
<td>&gt;75</td>
<td>135</td>
<td>2.10 (0.92–4.75)</td>
<td>0.077</td>
</tr>
<tr>
<td>Female</td>
<td>117</td>
<td>1.10 (0.83–1.47)</td>
<td>0.512</td>
</tr>
<tr>
<td>Hypertension</td>
<td>131</td>
<td>1.48 (1.09–2.00)</td>
<td>0.011*</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>60</td>
<td>1.62 (1.19–2.20)</td>
<td>0.002*</td>
</tr>
<tr>
<td>Smoker</td>
<td>63</td>
<td>1.04 (0.77–1.40)</td>
<td>0.822</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>13</td>
<td>0.91 (0.52–1.59)</td>
<td>0.732</td>
</tr>
<tr>
<td>Renal failure on dialysis</td>
<td>2</td>
<td>0.64 (1.60–2.59)</td>
<td>0.535</td>
</tr>
<tr>
<td>Heart failure</td>
<td>38</td>
<td>0.87 (0.61–1.24)</td>
<td>0.433</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>52</td>
<td>1.34 (0.97–1.84)</td>
<td>0.076</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>8</td>
<td>1.26 (0.62–2.55)</td>
<td>0.526</td>
</tr>
<tr>
<td>Prior ischemic stroke</td>
<td>51</td>
<td>1.13 (0.82–1.55)</td>
<td>0.462</td>
</tr>
<tr>
<td>Prior intracranial hemorrhage</td>
<td>10</td>
<td>2.41 (1.27–4.55)</td>
<td>0.007*</td>
</tr>
<tr>
<td>Antithrombotic therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No therapy</td>
<td>39</td>
<td>Reference</td>
<td>...</td>
</tr>
<tr>
<td>Aspirin</td>
<td>91</td>
<td>1.54 (1.06–2.24)</td>
<td>0.025*</td>
</tr>
<tr>
<td>Warfarin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First quartile TTR</td>
<td>20</td>
<td>2.39 (1.39–4.10)</td>
<td>0.002*</td>
</tr>
<tr>
<td>Second quartile TTR</td>
<td>14</td>
<td>1.54 (0.84–2.84)</td>
<td>0.166</td>
</tr>
<tr>
<td>Third quartile TTR</td>
<td>15</td>
<td>1.35 (0.74–2.45)</td>
<td>0.328</td>
</tr>
<tr>
<td>Fourth quartile TTR</td>
<td>14</td>
<td>1.20 (0.65–2.21)</td>
<td>0.560</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>2</td>
<td>0.76 (0.18–3.16)</td>
<td>0.700</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; HR, hazard ratio; and TTR, time in therapeutic range.

*P<0.05.
incidence of ICH among different treatment groups remained similar (Figure V in the online-only Data Supplement).

**Mortality**

In addition to ischemic stroke and ICH, 5019 patients died during the study period (18.3%/y). The overall high mortality indicated a high-risk population. Among these, patients on no therapy and on aspirin had the highest mortality rate: 17.0%/y and 37.1%/y, respectively. Although patients on warfarin had a lower overall mortality, there was a progressive decrease in mortality with decreasing TTR (first quartile, 11.4%/y; second quartile, 8.9%/y; third quartile, 5.4%/y; and fourth quartile, 4.6%/y). The annual mortality of patients on dabigatran was 1.8%/y (Figure VI in the online-only Data Supplement).

**Discussion**

To our knowledge, this is the first study to investigate the impact of TTR on the risk of stroke and ICH in Chinese patients with nonvalvular AF in a real-world clinical setting. In the present analysis, we first show that TTRs (median, 38.8%) were generally poor among Chinese AF patients. Second, the incidence of ischemic stroke decreased progressively with increasing TTR quartiles, ranging from 7.34%/y (first quartile) to 3.10%/y (fourth quartile), even on multivariate analysis. Indeed, patients on aspirin had a comparable incidence of ischemic stroke as those on warfarin in the lowest quartile of TTR (7.95%/y versus 7.34%/y), whereas the incidence of ischemic stroke in those on dabigatran was the lowest across all groups (2.24%/y). Third, the incidence of ICH decreased with increasing TTR quartiles among patients on warfarin, ranging from 1.37%/y (first quartile) to 0.74%/y (fourth quartile). Fourth, patients on dabigatran had the lowest incidence of ICH (0.32%/y), which was lower than that of patients on warfarin at the fourth quartile of TTR (ie, good quality anticoagulation control) or patients not receiving any antithrombotic therapy.

Despite a lower prevalence of AF in Chinese population (0.7%) in comparison with whites (1%-2%), the Chinese have a much higher overall disease burden because of its proportionally larger aged population. Lower risk of ischemic stroke than their white counterparts, as the same time, the baseline risk of ICH, the greatest barrier to anticoagulation therapy, was reportedly higher among Chinese, as well as in other Asian populations. Thereby, the use of long-term anticoagulation for stroke prevention in Chinese has been low.

Recent registry data of Chinese populations from Hong Kong and Beijing as well as subanalyses of data from the different NOAC trials focusing on Asian populations have demonstrated consistently that the risk of ischemic stroke in Chinese patients with AF was comparable with or even higher than that of whites. These findings are in accordance with the fact that globally, China is among the countries with the highest stroke rates. Although Chinese patients with AF receiving warfarin therapy have a higher risk of ICH compared with white counterparts, net clinical benefit analyses favor warfarin therapy over aspirin and no therapy in almost all combinations of CHA2DS2-VASc and HAS-BLED scores. Indeed, the net benefit of warfarin therapy is greatest among those at high risk of both stroke and ICH.

Another major stumbling block to stroke prevention in AF in Chinese population is the poor quality of anticoagulation control, as well as access to structured anticoagulation monitoring. In contemporary randomized trials, TTR varied greatly by country, but Asian populations (particularly Chinese) were among those with lowest TTRs. Outside trial settings, quality of anticoagulation would be expected to be even worse, as in the present cohort with the median TTR among Chinese patients with AF being as low as 38.8%. As the poor TTR could well be the result of poor standard of clinical practices, there are other plausible explanations. For instance, the optimal INR range of 2.0 to 3.0 is well established in white populations; however, given the higher baseline ICH risk among Asian particularly Chinese, there is a widespread perception that Asian/Chinese might need a lower target INR (eg, INR, 1.6–2.6) to avoid this deadliest complication, albeit the lack of good clinical evidence. Nonetheless, the so-called optimal INR in Asian/Chinese would not be available unless there is a large randomized controlled trials in Chinese to compare the efficacy and safety of warfarin in different ranges of INR. In addition, it is well known that many traditional Chinese medicines have been shown to
affect the human cytochrome P450 system. For instance, ginkgo, hypericum, and cranberry have been reported to augment the anticoagulation effect of warfarin, whereas ginseng and green tea inhibit its anticoagulation effect and have a significant interaction with warfarin. Although patients on warfarin are advised to avoid traditional Chinese medicine, we have shown previously that ≤30% of Chinese patients with AF on warfarin reported consumption of herbal ingredients which may potentially interact with warfarin. Interestingly, frequent herb users were more likely to have a poor TTR than infrequent users. In a recent clinical scoring scheme (SAME-TT2R2) [Sex, Age (<60 years), Medical History (at least 2 of the following: hypertension, diabetes, coronary artery disease/myocardial infarction, peripheral arterial disease, congestive heart failure, previous stroke, pulmonary disease, hepatic or renal disease), Treatment (interacting drugs eg amiodarone for rhythm control) (all 1 point), as well as current Tobacco use (2 points) and Race (non-Caucasian; 2 points)] designed to predict TTRs after initiation of warfarin, non-white race had been identified as one of the important contributors to poor TTR.

Why is TTR important? Patients on warfarin at low range of TTR have higher risk of adverse events including ischemic stroke, major bleeding, and mortality compared with those with high TTR, as thus, when warfarin is use, a recent European position article recommended that TTRs should be >70% for optimal efficacy and safety. Indeed, warfarin therapy may not confer any stroke prevention when the TTR is low. In a subanalysis of the Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE-W) trial, warfarin therapy was only superior to aspirin–clopidogrel combination therapy only among individuals with TTR ≥58%. Despite the poor overall TTR in the present cohort, warfarin therapy was still associated with lower annual incidence of ischemic stroke. With an average individual TTR ≥56.2%, patients on warfarin therapy still had 69% lower risk of ischemic stroke but without significant increase in ICH risk. As the reduction in ischemic stroke risk diminished with decreasing TTR, the risk of ICH increased progressively. Indeed, among patients at the first quartile (TTR <17.9%, ie, poor quality anticoagulation control), the risk of ischemic stroke was basically similar to those on aspirin therapy, but with the highest ICH risk among all group.

In contrast, patients on dabigatran not only had the lowest annual ischemic stroke risk among all groups but also had the lowest ICH risk. These findings concur with the subanalyses of the NOAC trials, where Asian patients treated with warfarin were at higher risk of ischemic stroke, major bleeding and ICH compared with their non-Asian counterparts.

Our study has several important clinical implications. First, as the efficacy and safety of warfarin therapy depend heavily on quality of anticoagulation, the decision and choice of anticoagulation should consider the anticipated TTR in Chinese patients, in addition to the risk of ischemic stroke (CHA₂DS₂-VASc score) and risk of ICH. Second, Chinese AF patients tend to attain a poor TTR when put on warfarin, a marker of reduced efficacy and added risks. For them, NOAC may be a safer alternative. Third, among Chinese patients with AF with poor TTR (ie, <17.9%), warfarin therapy may be associated with more risk than benefit.

Limitations
This study is limited by its registry-based and single-center observational design in primarily hospital-based patients. Because of the observational nature, the selection of antithrombotic strategies was not in a randomized fashion, and it is possible that residual confounding may be evident such that patients receiving different antithrombotic strategies, as well as patients on warfarin with different TTR, were in some ways different from each other. For instance, as indicated in Table 1, there were significant differences in baseline characteristics between patients on no therapy, aspirin, warfarin, and dabigatran. Despite statistical adjustments, potential impacts of residual confounding effects cannot be excluded. Nonetheless, the differences in mean CHA₂DS₂-VASc among these groups ranged only from 0.3 to 0.6. In addition, socioeconomic status might affect the choice of antithrombotic strategies and lead to potential selection bias. This is particularly important for dabigatran, which is currently a self-financing item in Hong Kong. Furthermore, although our data have demonstrated that dabigatran therapy and warfarin therapy with good TTR were associated with lower risks of ischemic stroke and ICH, given the observational nature, it could not be possible to ascertain causation. Nonetheless, although the gold standard to demonstrate treatment effects is a randomized placebo-control trial, which is not ethically possible at this point in time, a large real-world registry data serve as a good alternative. Although we carefully ascertained all strokes and ICH by careful examination of hospitalization records, laboratory and imaging results, patients with a milder form of stroke and ICH who were not hospitalized were not included.

In conclusion, the benefits of warfarin therapy for stroke prevention and ICH risk in Chinese patients with AF are closely dependent on the quality of anticoagulation control, as reflected by the TTR. Even at the top TTR quartile, warfarin therapy was associated with a higher stroke and ICH risk than dabigatran therapy.

Disclosures
Dr Lip has served as a consultant for Bayer, Astellas, Merck, AstraZeneca, Sanofi, BMS/Pfizer, Daiichi-Sankyo, Medtronic, Biotronik, Portola, and Boehringer Ingelheim and has been on the speakers’ bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, Medtronic, Daiichi-Sankyo, and Sanofi Aventis. Dr Tse has served as a consultant and advisory board member for Boehringer Ingelheim, Bayer, BMS/Pfizer, and Daiichi-Sankyo and has been on the speakers’ bureau for Boehringer Ingelheim, Bayer, and BMS/Pfizer. The other authors report no conflicts.

References


Ischemic Stroke and Intracranial Hemorrhage With Aspirin, Dabigatran, and Warfarin: Impact of Quality of Anticoagulation Control
Chi-Wai Ho, Mei-Han Ho, Pak-Hei Chan, Jo-Jo Hai, Emmanuel Cheung, Chun-Yip Yeung, Kui-Kai Lau, Koon-Ho Chan, Chu-Pak Lau, Gregory Y.H. Lip, Gilberto Ka-Kit Leung, Hung-Fat Tse and Chung-Wah Siu

Stroke. 2015;46:23-30; originally published online November 18, 2014;
doi: 10.1161/STROKEAHA.114.006476
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/46/1/23

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2015/05/22/STROKEAHA.114.006476.DC1
http://stroke.ahajournals.org/content/suppl/2016/04/07/STROKEAHA.114.006476.DC2

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/
Supplemental Figures

Supplemental Figure I

10,195 patients
From 1997-2011

Prosthetic valves
Mitral stenosis
Incomplete data

9,727 patients

CHA2DS2-VASC ≤ 1

8,361 patients

8,754 patients

500 patients on
dabigatran
From 2010-2013

Incomplete data

467 patients

CHA2DS2-VASC ≤ 1

393 patients

Supplemental Figure I. Study population
Supplemental Figure II. Kaplan-Meier estimates of ischemic stroke-free survival in Chinese AF patients receiving warfarin with TTR≥70% and dabigatran.
Supplemental Figure III

Supplemental Figure III. Relation between different antithrombotic therapies and the annual risk of ischemic stroke in Chinese AF patients before and after 2008

Q1: TTR at 1st quartile; Q2: TTR at 2nd quartile; Q3: TTR at 3rd quartile; and
Q4: TTR at 4th quartile
Supplemental Figure IV. Relation between different antithrombotic therapies and the annual risk of intracranial hemorrhage in Chinese AF patients before and after 2008

Q1: TTR at 1st quartile; Q2: TTR at 2nd quartile; Q3: TTR at 3rd quartile; and
Q4: TTR at 4th quartile
Supplemental Figure V. Relation between different antithrombotic therapies and the annual risk of intracranial hemorrhage in Chinese AF patients after excluding patients with prior history of intracranial hemorrhage. Q1: TTR at 1st quartile; Q2: TTR at 2nd quartile; Q3: TTR at 3rd quartile; and Q4: TTR at 4th quartile.
Supplemental Figure VI. Kaplan-Meier estimates of survival in Chinese AF patients receiving different antithrombotic therapy

Log Rank: 1,499, P<0.0001

Dabigatran
4th Quartile TTR
3rd Quartile TTR
2nd Quartile TTR
1st Quartile TTR

Aspirin
No therapy
Abstract 2

Ischemic Stroke and Intracranial Hemorrhage
With Aspirin, Dabigatran, and Warfarin
Impact of Quality of Anticoagulation Control

Chi-Wai Ho, MBBS*; Mei-Han Ho, MBBS*; Pak-Hei Chan, MBBS; Jo-Jo Hai, MBBS; Emmanuel Cheung, MBBS; Chun-Yip Yeung, MBBS; Kui-Kai Lau, MBBS; Koon-Ho Chan, MD; Chu-Pak Lau, MD; Gregory Y.H. Lip, MD; Gilberto Ka-Kit Leung, MS; Hung-Fat Tse, MD, PhD; Chung-Wah Siu, MD

(Stroke. 2015;46:23-30.)

Key Words: atrial fibrillation ■ intracranial hemorrhages

Background and Objectives

Stroke and intracranial hemorrhage are major causes of mortality and disability, and optimal anticoagulation control is a cornerstone of prevention. The time in therapeutic range (TTR) is a widely used quality measure for anticoagulation control. Whether comparable TTRs indicate comparable levels of anticoagulation control is unclear. We examined the association between TTR quartiles and the incidence of ischemic stroke and intracranial hemorrhage among patients with atrial fibrillation.

Methods

We conducted a retrospective analysis of the cohort of patients with atrial fibrillation from the International Normalized Ratio, Elderly (>65 years), Drugs/Alcohol Concomitantly, 2.2±0.9. The incidence of ischemic stroke and intracranial hemorrhage were compared among patients with TTR at different quartiles, with univariate and multivariate analyses. The primary endpoint was the annual incidence of ischemic stroke and intracranial hemorrhage, analyzed using the Kaplan-Meier method and Cox proportional hazards regression.

Results

The incidence of ischemic stroke and intracranial hemorrhage was lowest among patients with TTR at the top quartile, and highest among those with TTR at the bottom quartile. The hazard ratios for ischemic stroke and intracranial hemorrhage were 7.74 (95% CI, 2.24–27.34) and 2.20 (95% CI, 1.05–4.63), respectively, for TTR at the bottom quartile compared with TTR at the top quartile.

Conclusions

Our findings suggest that comparable TTRs do not necessarily indicate comparable levels of anticoagulation control and may not reflect the effective anti-platelet or anti-thrombotic effect of anticoagulant therapy.
Abstract 3

Prolonged QTc Interval Predicts Poststroke Paroxysmal Atrial Fibrillation

Takao Hoshino, MD, PhD; Takehiko Nagao, MD, PhD; Tsuyoshi Shiga, MD, PhD; Kenji Maruyama, MD, PhD; Sono Toi, MD, PhD; Satoko Mizuno, MD; Kentaro Ishizuka, MD; Satoru Shimizu, MD, PhD; Shinchiro Uchiyama, MD, PhD; Kazuo Kitagawa, MD, PhD

(Stroke. 2015;46:71-76.)

Key Words: atrial fibrillation • electrocardiography • stroke

배경과 목적
발작성 심방세동(paroxysmal atrial fibrillation, PAF)은 급성혈
혈뇌졸중 환자에서 때때로 발견하기 어렵다. 이 연구는 심박수로
보정한 QT 간격(QT interval corrected for heart rate, QTc
interval) 연장의 급성혈뇌졸중 이후 PAF 발생에 대한 예측도
(predictive value)을 평가하는 것을 목표로 하였다.

방법
관찰 뇌졸중 환자등록자료로부터 연속적으로 추출한 972명의 급
성뇌졸중 환자를 등록하였다. 제외기준은 다음과 같았다: (1)
초기 12-유도 심전도에서 AF (n=171); (2) 이전에 진단된 PAF
(n=47); (3) 심장박동조율기를 사용(n=10). 환자 972명 중 744명(평
균 연령, 67.6세; 남성, 62.6%)을 본선 대상으로 하였다. 환자의
입상적 특징 및 심전도에서 PAF 유무에 따른 12-유도 심전도 결
과를 비교하여, 뇌졸중 이후 PAF의 예측 인자를 판별하기 위한 다
중 로지스틱 회귀분석을 시행하였다.

결과
뇌졸중 이후 심장 조사로 환자 744명 중 69명(9.3%)에서 새로운
PAF 증례를 찾을 수 있었다. QTc 길이는 PAF가 있는 환자에서
PAF가 없는 환자에 비하여 유의하게 길었다(436 대 417 ms;