Validation of a Modified CHA₂DS₂-VASc Score for Stroke Risk Stratification in Asian Patients With Atrial Fibrillation

A Nationwide Cohort Study

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Background and Purpose—The age threshold for an increased stroke risk for patients with atrial fibrillation may be different for Asians and non-Asians. We hypothesized that a modified CHA₂DS₂-VASc (congestive heart failure, hypertension, age ≥75, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65–74 years, female) scheme, mCHA₂DS₂-VASc, which assigned one point for patients aged 50 to 74 years, may perform better than CHA₂DS₂-VASc score for stroke risk stratification in Asians.

Methods—This study used the Taiwan National Health Insurance Research Database, which included 224 866 newly diagnosed atrial fibrillation patients. The predictive accuracies of ischemic stroke of CHA₂DS₂-VASc and mCHA₂DS₂-VASc scores were compared among 124 271 patients without antithrombotic therapies. From the whole cohort, 15 948 patients had a CHA₂DS₂-VASc score 0 (males) or 1 (females), and 8654 patients had an mCHA₂DS₂-VASc score 1 (males) or 2 (females). The latter were categorized into 3 groups, that is, no treatment, antiplatelet therapy, and warfarin, and the risks of ischemic stroke and intracranial hemorrhage (ICH) were compared.

Results—During a follow-up of 538 653 person-years, 20 008 patients experienced ischemic stroke. The mCHA₂DS₂-VASc performed better than CHA₂DS₂-VASc score in predicting ischemic stroke assessed by C indexes and net reclassification index. For 8654 patients having an mCHA₂DS₂-VASc score of 1 (males) or 2 (females) because of the resetting of the age threshold, use of warfarin was associated with a 30% lower risk of ischemic stroke and a similar risk of ICH compared with nontreatment. Net clinical benefit analyses also favored the use of warfarin in different weighted models.

Conclusions—In this Asian atrial fibrillation cohort, the mCHA₂DS₂-VASc score performed better than the CHA₂DS₂-VASc and would further identify atrial fibrillation patients who may derive a positive net clinical benefit from oral anticoagulation. (Stroke. 2016;47:2462-2469. DOI: 10.1161/STROKEAHA.116.013880.)

Key Words: age • atrial fibrillation • CHA₂DS₂-VASc score • ischemic stroke • modified CHA₂DS₂-VASc score

Atrial fibrillation (AF) confers a 5-fold increased risk of stroke compared with patients without AF. The risk of AF-associated stroke is not homogeneous and depends on patients’ age and comorbidities, which have resulted in the development of clinical scores to aid stroke risk stratification and guide the use of oral anticoagulation (OAC) for stroke prevention. Currently, the CHA₂DS₂-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65–74 years, female) score is recommended by guidelines for stroke risk stratification in AF and has been shown to be better than the older CHADS₂ (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and prior stroke or transient ischemic attack) score for stroke risk stratification among Asian AF patients.

Because age is an important driver of ischemic stroke for AF patients, the CHA₂DS₂-VASc scheme assigns 1 point for those aged 50 to 74 years. However, the age threshold for an increased stroke risk for patients with AF may be different for Asians and non-Asians. We hypothesized that a modified CHA₂DS₂-VASc scheme, mCHA₂DS₂-VASc, which assigned one point for patients aged 50 to 74 years, may perform better than CHA₂DS₂-VASc score for stroke risk stratification in Asians. This study used the Taiwan National Health Insurance Research Database, which included 224 866 newly diagnosed atrial fibrillation patients. The predictive accuracies of ischemic stroke of CHA₂DS₂-VASc and mCHA₂DS₂-VASc scores were compared among 124 271 patients without antithrombotic therapies. From the whole cohort, 15 948 patients had a CHA₂DS₂-VASc score 0 (males) or 1 (females), and 8654 patients had an mCHA₂DS₂-VASc score 1 (males) or 2 (females). The latter were categorized into 3 groups, that is, no treatment, antiplatelet therapy, and warfarin, and the risks of ischemic stroke and intracranial hemorrhage (ICH) were compared.

Results—During a follow-up of 538 653 person-years, 20 008 patients experienced ischemic stroke. The mCHA₂DS₂-VASc performed better than CHA₂DS₂-VASc score in predicting ischemic stroke assessed by C indexes and net reclassification index. For 8654 patients having an mCHA₂DS₂-VASc score of 1 (males) or 2 (females) because of the resetting of the age threshold, use of warfarin was associated with a 30% lower risk of ischemic stroke and a similar risk of ICH compared with nontreatment. Net clinical benefit analyses also favored the use of warfarin in different weighted models.

Conclusions—In this Asian atrial fibrillation cohort, the mCHA₂DS₂-VASc score performed better than the CHA₂DS₂-VASc and would further identify atrial fibrillation patients who may derive a positive net clinical benefit from oral anticoagulation. (Stroke. 2016;47:2462-2469. DOI: 10.1161/STROKEAHA.116.013880.)

Key Words: age • atrial fibrillation • CHA₂DS₂-VASc score • ischemic stroke • modified CHA₂DS₂-VASc score

Atrial fibrillation (AF) confers a 5-fold increased risk of stroke compared with patients without AF. The risk of AF-associated stroke is not homogeneous and depends on patients’ age and comorbidities, which have resulted in the development of clinical scores to aid stroke risk stratification and guide the use of oral anticoagulation (OAC) for stroke prevention. Currently, the CHA₂DS₂-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65–74 years, female) score is recommended by guidelines for stroke risk stratification in AF and has been shown to be better than the older CHADS₂ (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and prior stroke or transient ischemic attack) score for stroke risk stratification among Asian AF patients.

Because age is an important driver of ischemic stroke for AF patients, the CHA₂DS₂-VASc scheme assigns 1 point for those aged 50 to 74 years.
patients aged between 65 and 74 years and 2 points for those aged ≥75 years. However, the age threshold for an increased risk of ischemic stroke for Asians may be lower than that of Caucasians. For Asian AF patients with a CHA2DS2-VASc score of 0 (males) or 1 (females) aged between 50 and 64 years, the annual risk of ischemic stroke was =1.78%/y, which exceeds the threshold for the initiation of OACs; 1%/y, especially if non–vitamin K antagonist OACs (NOACs) are used (0.9%/y). However, whether resetting the age threshold at 50 years could refine current clinical stroke risk stratification for Asian AF patients is unknown.

In the present study, we propose a simple, modified CHA2DS2-VASc (mCHA2DS2-VASc) score by resetting the age threshold at 50 years. We hypothesized that the mCHA2DS2-VASc score may perform better than CHA2DS2-VASc score for stroke risk stratification in Asians. Second, we aimed to investigate whether the mCHA2DS2-VASc score could further identify AF patients who may derive benefits from OAC use among those patients with a CHA2DS2-VASc score of 0 (males) or 1 (females).

**Methods**

**Database**

The study protocol of the present study is similar to our previous publications. This study used the well-validated National Health Insurance Research Database (NHIRD) released by the Taiwan National Health Research Institutes. The National Health Insurance system is a mandatory universal health insurance program that offers comprehensive medical care coverage to all Taiwanese residents. NHIRD consists of detailed healthcare data from >23 million enrollees, representing >99% of Taiwan’s population. In this cohort data set, the patients’ original identification numbers have been encrypted to protect their privacy, but the encrypting procedure was consistent, so that a linkage of the claims belonging to the same patient was feasible within the National Health Insurance database and can be followed continuously. The large sample size of this database provided a good opportunity to study whether resetting age threshold at 50 years could refine clinical risk stratification for Asian AF patients.

Information about important comorbid conditions of each individual was retrieved from the medical claims based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes. We defined patients with a certain disease only when it was a discharge diagnosis or confirmed more than twice in the outpatient department. The diagnostic accuracies of important comorbidities in NHIRD, such as hypertension, diabetes mellitus, heart failure, myocardial infarction, hyperlipidemia, and chronic obstructive pulmonary disease, have been validated before.

Information about the medications the patients used was retrieved from the NHIRD using the specific code of each drug registered by physicans responsible for the treatment of the patients for the purpose of getting reimbursement from the National Health Insurance system.

**Calculation of CHA2DS2-VASc and mCHA2DS2-VASc Scores**

The CHA2DS2-VASc score was calculated by assigning 1 point each for age between 65 and 74 years, history of hypertension, diabetes mellitus, recent cardiac failure, vascular disease (myocardial infarction or peripheral artery disease), and female sex and 2 points each for a history of a stroke, transient ischemic attack, or age ≥75 years. The mCHA2DS2-VASc score was calculated by assigning 1 point each for age between 50 and 74 years, history of hypertension, diabetes mellitus, recent cardiac failure, vascular disease (myocardial infarction or peripheral artery disease), and female sex and 2 points each for a history of a stroke, transient ischemic attack, or age ≥75 years (Table 1).

**Definition of Clinical End Point and Calculation of Net Clinical Benefit**

The principal clinical end point was the occurrence of ischemic stroke, with concomitant imaging studies of the brain, including computed tomography or magnetic resonance imaging. The accuracy of diagnosis of ischemic stroke in Taiwan’s NHIRD has been reported to be 94%. Another validation study also demonstrated that the diagnostic accuracy of ischemic stroke in NHIRD was high, with the positive predictive value and sensitivity of 88.4% and 97.3%, respectively. The principal safety end point was the occurrence of intracranial hemorrhage (ICH), necessitating admissions to intensive care units.

The net clinical benefit (NCB) for the use of warfarin or antiplatelet therapy compared with no treatment was calculated using the formula: (ischemic stroke rate on no treatment–ischemic stroke rate on anti-thrombotic therapy)–weighting factor×(ICH rate on anti-thrombotic therapy–ICH rate on no treatment).

The weighting factor reflects the relative impact, in terms of death and disability, of an ICH while receiving warfarin or antiplatelet agents versus experiencing an ischemic stroke while on no treatment.

The NCB with 95% confidence intervals (CI) was calculated from rate differences and standard errors estimated using Poisson regression based on the weights from Singer et al., Connolly et al., and Lip et al. A positive NCB favors treatment (ie, warfarin) when compared with no treatment.

**Statistical Analysis**

After a test of statistical normality, data are presented as means and standard deviation or medians and interquartile ranges for continuous variables and as n (%) for categorical variables. Incidence rates of ischemic stroke and ICH were calculated from dividing the number of event by person-time at risk, with the 95% CI estimated by exact binomial probabilities. The risks of ischemic stroke and ICH were assessed using the Cox regression analysis.

We assessed the predictive accuracies of the CHA2DS2-VASc and mCHA2DS2-VASc scores by calculating C indexes based on the receiver-operating characteristic curve. The areas under the receiver-operating characteristic curves of these 2 scoring systems were compared using DeLong’s test. The net reclassification index comparing the CHA2DS2-VASc and mCHA2DS2-VASc scores was also calculated. All statistical significances were set at a P<0.05.

The present study was approved by the Institutional Review Board at Taipei Veterans General Hospital, Taipei, Taiwan.
Table 1. Calculations of CHA2DS2-VASc and mCHA2DS2-VASc Schemes

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>CHA2DS2-VASc Score</th>
<th>mCHA2DS2-VASc Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥75 y</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Stroke/transient ischemic attack</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disease (prior myocardial infarction, peripheral artery disease)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Age 65–74 y</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Age 50–74 y</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Sex category (female sex)</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

CHA2DS2-VASc indicates congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65–74 years, female; and modified CHA2DS2-VASc (mCHA2DS2-VASc), congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 50–74 years, female.

Results

Baseline Characteristics of Study Patients

Baseline characteristics of the study cohort are shown in Table 2. The mean age of patients was 72.0±13.9 years, and 54.3% were male. The median values (interquartile range) of the CHA2DS2-VASc and mCHA2DS2-VASc scores were 3 (2–5) and 4 (2–5), respectively. Hypertension was the most prevalent comorbidity in 56.8% of patients.

Table 2. Baseline Characteristics of AF Patients Without Antithrombotic Therapies (n=124 271)

<table>
<thead>
<tr>
<th>Variables</th>
<th>n=124 271</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>72.0±13.9</td>
</tr>
<tr>
<td>Age 50- to 64-y old, n (%)</td>
<td>19 948 (16.1)</td>
</tr>
<tr>
<td>Age 65- to 74-y old, n (%)</td>
<td>33 942 (27.3)</td>
</tr>
<tr>
<td>Age ≥75-y old, n (%)</td>
<td>60 668 (48.8)</td>
</tr>
<tr>
<td>Sex (male), n (%)</td>
<td>67 461 (54.3)</td>
</tr>
<tr>
<td>Underlying diseases, n (%) (components of the CHA2DS2-VASc scores)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>70 557 (56.8)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>28 915 (23.3)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>46 821 (37.7)</td>
</tr>
<tr>
<td>Previous stroke/transient ischemic attack</td>
<td>38 844 (28.0)</td>
</tr>
<tr>
<td>Previous vascular diseases</td>
<td>13 722 (11.0)</td>
</tr>
<tr>
<td>CHA2DS2-VASc score, median (interquartile range)</td>
<td>3 (2–5)</td>
</tr>
<tr>
<td>mCHA2DS2-VASc score, median (interquartile range)</td>
<td>4 (2–5)</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; CHA2DS2-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65–74 years, female; and modified CHA2DS2-VASc (mCHA2DS2-VASc), congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 50–74 years, female.

CHA2DS2-VASc, mCHA2DS2-VASc, and the Risk of Ischemic Stroke Among Patients Without Antithrombotic Treatment

During a follow-up of 538 653 person-years, 21 008 patients (16.9%) sustained an ischemic stroke with an annual risk of 3.9%. Both the CHA2DS2-VASc and mCHA2DS2-VASc scores were significant predictors of ischemic stroke with a hazard ratio (95% CI) of 1.167 (1.159–1.176) and 1.164 (1.155–1.173) per 1 point increment of the CHA2DS2-VASc and mCHA2DS2-VASc scores, respectively. The incidences (per 100 person-years) of ischemic stroke of patients stratified by CHA2DS2-VASc and mCHA2DS2-VASc scores are shown in Table 3. For score=0 in males or 1 in females, ischemic stroke rates using the CHA2DS2-VASc score were 1.2 per 100 person-years or with the mCHA2DS2-VASc score, 0.46 for males and 0.63 for females.

Figure II in the online-only Data Supplement shows the receiver-operating characteristic curves of CHA2DS2-VASc and mCHA2DS2-VASc scores in predicting ischemic stroke. The C indexes based on areas under the curve for the CHA2DS2-VASc and mCHA2DS2-VASc scores in predicting ischemic stroke were 0.689 (95% CI 0.684–0.694) and 0.708 (95% CI 0.703–0.712), respectively. The difference was statistically significant in favor of the mCHA2DS2-VASc score (DeLong test P<0.0001). The mCHA2DS2-VASc score also improved the net reclassification index by 3.39% (95% CI 2.16%–4.59%) compared with the CHA2DS2-VASc score (P<0.0001).

Antithrombotic Strategies With a CHA2DS2-VASc Score of 0 (Males) or 1 (Females), Having an mCHA2DS2-VASc Score of 0 (Males) or 2 (Females)

Among 15 948 patients with a CHA2DS2-VASc score of 0 (males) or 1 (females), there were 8654 patients having an mCHA2DS2-VASc score of 0 (males) or 2 (females) because of the resetting of the age threshold. The latter were divided into 3 groups based on the antithrombotic strategies, that is, no treatment (n=6114), antiplatelet therapy (1433), and warfarin (1107). The risks of ischemic stroke and ICH on warfarin and antiplatelet agents compared with no antithrombotic therapy are shown in Table 4.

Compared with patients without antithrombotic therapy, the use of antiplatelet agents was not associated with a lower risk of ischemic stroke (adjusted hazard ratio 1.08 [95% CI 0.94–1.24; P=0.275]) but significantly increased the risk of ICH (1.77 [95% CI 1.29–2.41; P<0.001]; Table 4). For the patients receiving warfarin, the risk of ischemic stroke was lower compared with no antithrombotic therapy (adjusted hazard ratio of 0.70 [95% CI 0.59–0.84; P<0.001]), with no significant difference in the risk of ICH (0.95 [95% CI 0.61–1.46; P=0.804]; Table 4. Figure 4 shows the cumulative incidence curves for ischemic stroke (Figure [A]), ICH (Figure [B]), and ischemic stroke/ICH (Figure [C]) in different treatment groups.

The results of NCB analyses for each treatment according to different weighted models are shown in Table 5. The NCBs were consistently positive for warfarin use and negative for antiplatelet drugs, irrespective of different weighted models used. The NCB for warfarin versus antiplatelet therapy was also positive, in favor of OAC.
mCHA2DS2-VASc score performs significantly better than the CHA2DS2-VASc score (using C indexes and net reclassification index) and can further identify Asian AF patients who may derive benefits from stroke prevention. Second, we show that the use of OAC results in a positive NCB among low-risk patients in whom OACs could be clearly omitted.25 The ability of a scoring scheme to identify AF patients who are truly low risk of ischemic stroke is an even more important issue in Asians because this risk among Asians may be much higher than that among Caucasians, as demonstrated in registry studies and randomized trials.10,26–30

All clinical risk scoring systems have broadly comparable predictive value for identifying high-risk patients who sustain stroke events. Rather than a categorized approach to stroke risk stratification focusing on high-risk patients, a simple approach to thromboprophylaxis is to initially identify truly low-risk patients in whom OACs could be clearly omitted.25 The ability of a scoring scheme to identify AF patients who are truly low risk of ischemic stroke is an even more important issue in Asians because this risk among Asians may be much higher than that among Caucasians, as demonstrated in registry studies and randomized trials.10,26–30

Indeed, the CHA2DS2-VASc score has been shown to consistently better than the older CHADS2 score in identifying low-risk patients, even among Asian patients.31 Take our previous study for example, among 25 286 Asian AF patients with a CHADS2 score of 0, the CHA2DS2-VASc scores of these subjects ranged from 0 to 3, and the annual risk of ischemic stroke can be as high as 4.47%.4 However, the risk of ischemic stroke was still 1.15%/y for patients with a CHA2DS2-VASc score of 0, which is above the suggested threshold for the initiation of NOACs (0.9%/y).8

In our previous study, we suggested that the age threshold in Asian AF patients for an increased risk (>1%/y) of ischemic stroke could perhaps be lowered to 50 years.3 Although the detailed mechanism(s) behind the higher risk of ischemic stroke for younger AF patients in Asians remained unknown, atherosclerosis may play a more important role of ischemic stroke in Chinese AF patients than in Caucasian patients. Indeed, China and other Asian countries are among the countries with the highest incidence of stroke,32 and intracranial atherosclerosis is common among Chinese patients who experienced ischemic event.33 Further prospective studies are necessary to investigate this issue.

In the present study, we further demonstrate that the mCHA2DS2-VASc score (by giving 1 point to age 50–74 years) could clearly identify Asians patients who were truly low risk for ischemic stroke. Indeed, the annual risks of ischemic stroke for males with an mCHA2DS2-VASc score of 0 and females with an mCHA2DS2-VASc score 1 were 0.9%/y and 0.63%, respectively, and thus, OACs could be clearly omitted for this population. In contrast, the annual risks of ischemic stroke for males with a CHA2DS2-VASc score of 0 and females with a CHA2DS2-VASc score of 1 were 1.21% and 1.18%, respectively.

Table 3. Risk of Ischemic Stroke in Untreated Patients Stratified by CHA2DS2-VASc and mCHA2DS2-VASc Scores

<table>
<thead>
<tr>
<th>Groups</th>
<th>Number of Patients</th>
<th>Number of Ischemic Stroke</th>
<th>Person-Years</th>
<th>Incidence*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHA2DS2-VASc scores</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>6487</td>
<td>635</td>
<td>52680</td>
<td>1.21</td>
</tr>
<tr>
<td>1</td>
<td>13328</td>
<td>2138</td>
<td>98835</td>
<td>2.16</td>
</tr>
<tr>
<td>Males</td>
<td>9441</td>
<td>1683</td>
<td>60337</td>
<td>2.79</td>
</tr>
<tr>
<td>Females</td>
<td>4387</td>
<td>455</td>
<td>38498</td>
<td>1.18</td>
</tr>
<tr>
<td>2</td>
<td>19538</td>
<td>3668</td>
<td>104398</td>
<td>3.51</td>
</tr>
<tr>
<td>3</td>
<td>23114</td>
<td>4577</td>
<td>100358</td>
<td>4.56</td>
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<tr>
<td>4</td>
<td>21996</td>
<td>4200</td>
<td>78620</td>
<td>5.34</td>
</tr>
<tr>
<td>5</td>
<td>17386</td>
<td>2738</td>
<td>51915</td>
<td>5.27</td>
</tr>
<tr>
<td>6</td>
<td>12118</td>
<td>1697</td>
<td>30570</td>
<td>5.55</td>
</tr>
<tr>
<td>7</td>
<td>6892</td>
<td>910</td>
<td>15458</td>
<td>5.89</td>
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<tr>
<td>8</td>
<td>2529</td>
<td>363</td>
<td>5054</td>
<td>7.18</td>
</tr>
<tr>
<td>9</td>
<td>383</td>
<td>82</td>
<td>765</td>
<td>10.72</td>
</tr>
<tr>
<td>Total</td>
<td>124271</td>
<td>21008</td>
<td>538653</td>
<td>3.90</td>
</tr>
</tbody>
</table>

| mCHA2DS2-VASc scores | | | | |
|----------------------|---------------------------|--------------|------------|
| 0                    | 2854                      | 136          | 29600      | 0.46       |
| 1                    | 11071                     | 1629         | 82183      | 2.03       |
| Males                | 9165                      | 1499         | 61397      | 2.44       |
| Females              | 1906                      | 130          | 20786      | 0.63       |
| 2                    | 20473                     | 3706         | 114423     | 3.24       |
| 3                    | 24899                     | 4918         | 115205     | 4.27       |
| 4                    | 23692                     | 4539         | 87109      | 5.21       |
| 5                    | 18466                     | 2934         | 55670      | 5.27       |
| 6                    | 12767                     | 1754         | 32273      | 5.43       |
| 7                    | 7089                      | 952          | 16214      | 5.87       |
| 8                    | 2577                      | 358          | 5211       | 6.87       |
| 9                    | 383                       | 82           | 765        | 10.72      |
| Total                | 124271                    | 21008        | 538653     | 3.90       |

CHADS2-VASc indicates congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65–74 years, female; and modified CHA2DS2-VASc (mCHA2DS2-VASc), congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 50–74 years, female.

*Number of ischemic stroke per 100 person-years of follow-up.

Discussion

In this nationwide study, we propose and validate a mCHA2DS2-VASc scheme because of the resetting of the age threshold for stroke risk stratification among Asian AF patients (specifically, Taiwanese Chinese). Our results demonstrate that the mCHA2DS2-VASc score performs significantly better than the CHA2DS2-VASc score (using C indexes and net reclassification index) and can further identify Asian AF patients who may derive benefits from stroke prevention. Second, we show that the use of OAC results in a positive NCB among AF patients aged 50 to 64 years with mCHA2DS2-VASc score 1 for males or 2 for females; in contrast, antiplatelet therapy resulted in a negative NCB.

Improved convenience and safety of NOACs compared with vitamin K antagonists have lowered the threshold for initiating OACs for AF patients for stroke prevention.8 The tipping point threshold when balancing stroke reduction against serious bleeding for initiating OAC is a stroke rate of 1.7%/y when vitamin K antagonists are used or 0.9%/y with the NOACs.8 The treatment threshold with vitamin K antagonist may even be lower with good quality anticoagulation control, where a high time in therapeutic range (>70%) is achieved, given that a high time in therapeutic range is associated with best efficacy and safety related to vitamin K antagonists.22–24

All clinical risk scoring systems have broadly comparable predictive value for identifying high-risk patients who sustain stroke events. Rather than a categorized approach to stroke risk stratification focusing on high-risk patients, a simple approach to thromboprophylaxis is to initially identify truly low-risk patients in whom OACs could be clearly omitted.25 The ability of a scoring scheme to identify AF patients who are truly low risk of ischemic stroke is an even more important issue in Asians because this risk among Asians may be much higher than that among Caucasians, as demonstrated in registry studies and randomized trials.10,26–30

Indeed, the CHA2DS2-VASc score has been shown to consistently better than the older CHADS2 score in identifying low-risk patients, even among Asian patients.31 Take our previous study for example, among 25 286 Asian AF patients with a CHADS2 score of 0, the CHA2DS2-VASc scores of these subjects ranged from 0 to 3, and the annual risk of ischemic stroke can be as high as 4.47%.4 However, the risk of ischemic stroke was still 1.15%/y for patients with a CHA2DS2-VASc score of 0, which is above the suggested threshold for the initiation of NOACs (0.9%/y).8

In our previous study, we suggested that the age threshold in Asian AF patients for an increased risk (>1%/y) of ischemic stroke could perhaps be lowered to 50 years.3 Although the detailed mechanism(s) behind the higher risk of ischemic stroke for younger AF patients in Asians remained unknown, atherosclerosis may play a more important role of ischemic stroke in Chinese AF patients than in Caucasian patients. Indeed, China and other Asian countries are among the countries with the highest incidence of stroke,32 and intracranial atherosclerosis is common among Chinese patients who experienced ischemic event.33 Further prospective studies are necessary to investigate this issue.

In the present study, we further demonstrate that the mCHA2DS2-VASc score (by giving 1 point to age 50–74 years) could clearly identify Asians patients who were truly low risk for ischemic stroke. Indeed, the annual risks of ischemic stroke for males with an mCHA2DS2-VASc score of 0 and females with an mCHA2DS2-VASc score 1 were 0.46% and 0.63%, respectively, and thus, OACs could be clearly omitted for this population. In contrast, the annual risks of ischemic stroke for males with a CHA2DS2-VASc score of 0 and females with a CHA2DS2-VASc score of 1 were 1.21% and 1.18%, respectively.
Table 4. Risk of Ischemic Stroke and ICH Stratified Based on the Strategies for Stroke Prevention Among Patients Aged 50 to 64 Years (CHA$_2$DS$_2$-VASc Score 0, mCHA$_2$DS$_2$-VASc Score 1 for Males; CHA$_2$DS$_2$-VASc Score 1, mCHA$_2$DS$_2$-VASc Score 2 for Females)

<table>
<thead>
<tr>
<th>Stroke Prevention Strategy</th>
<th>n</th>
<th>Incidence*</th>
<th>Adjusted HR† (95% CI)</th>
<th>P Value</th>
<th>Incidence*</th>
<th>Adjusted HR† (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No antithrombotic therapy (reference group)</td>
<td>6114</td>
<td>2.02</td>
<td>Reference</td>
<td>…</td>
<td>0.27</td>
<td>Reference</td>
<td>…</td>
</tr>
<tr>
<td>Antiplatelet drugs</td>
<td>1433</td>
<td>2.11</td>
<td>1.08 (0.94–1.24)</td>
<td>0.275</td>
<td>0.44</td>
<td>1.77 (1.29–2.41)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Warfarin</td>
<td>1107</td>
<td>1.43</td>
<td>0.70 (0.59–0.84)</td>
<td>&lt;0.001</td>
<td>0.25</td>
<td>0.95 (0.61–1.46)</td>
<td>0.804</td>
</tr>
</tbody>
</table>

CHA$_2$DS$_2$-VASc indicates congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65–74 years, female; CI, confidence interval; ICH, intracranial hemorrhage; and modified CHA$_2$DS$_2$-VASc (mCHA$_2$DS$_2$-VASc), congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 50–74 years, female.

*Per 100 person-years of follow-up.

†Adjusted for age and sex.

Clinical Implications

For the 8654 patients with a CHA$_2$DS$_2$-VASc score of 0 (males) or 1 (females) having an mCHA$_2$DS$_2$-VASc score of 1 (males) or 2 (females) because of the resetting of the age threshold, untreated patients had an ischemic stroke rate of 2.02%/y, and the use of warfarin was associated with a 30% lower risk of ischemic stroke and a similar risk of ICH versus nontreatment (0.25%/y with warfarin versus 0.27% for nontreatment). The observed low risk of ICH among warfarin users in a low CHA$_2$DS$_2$-VASc score in the present study is consistent with a previous report.34 The results of our NCB analyses also favored the use of warfarin compared with nontreatment (or aspirin), irrespective of different weighted models, whereas antiplatelet therapy had a negative NCB compared with nontreatment. Based on the results of NCB analyses, the number needed to treat with warfarin use ranged from 152 to 159 compared with non-treatment and ranged from 77 to 101 compared with antiplatelet drugs in different weight models. Because 54.3% of patients with a CHA$_2$DS$_2$-VASc score of 0 (males) or 1 (females) would have an mCHA$_2$DS$_2$-VASc score of 1 (males) or 2 (females) in our cohort, using the mCHA$_2$DS$_2$-VASc score would approximately identify an additional 54 people who may get benefits with warfarin use for every 100 patients with a CHA$_2$DS$_2$-VASc score of 0 (males) or 1 (females) screened.

Based on the findings of the present study, we proposed an algorithm for stroke prevention using the mCHA$_2$DS$_2$-VASc score for Asian AF patients (Figure III in the online-only Data Supplement). Asian AF patients with an mCHA$_2$DS$_2$-VASc score of 0 (males) or 1 (females) are truly low risk, and OACs could be clearly omitted. For male patients with an mCHA$_2$DS$_2$-VASc score ≥1 and female patients with an mCHA$_2$DS$_2$-VASc score ≥2, OACs should be prescribed, and NOACs are the preferred option because the risk of warfarin-related ICH and major bleeding is higher in Asians compared with non-Asians.35,36

Limitations

There are several limitations of the present study. First, the types of AF (paroxysmal or nonparoxysmal) were not available from this nationwide data set. Although the risk of stroke did not differ between patients with paroxysmal or non-paroxysmal AF in previous studies,37,38 recent analyses show that the risk of ischemic stroke was higher in patients with nonparoxysmal AF compared with those with paroxysmal AF.39 However, current guidelines do not consider AF type as a determinant of OAC use in the presence of stroke risk factors. Second, the diagnosis of AF and occurrence of ischemic stroke were based on the diagnostic codes registered by the physicians responsible for the treatments of patients; nonetheless, the accuracy of diagnosis of AF and ischemic stroke in Taiwan’s NHIRD has been previously validated to be high.14,16–18 Third, we do not have time in therapeutic range data available for the warfarin-treated patients, but despite this, a positive NCB was evident even with one stroke risk factor, consistent with prior studies.21,40 Fourth, the NCB of each treatment was not analyzed based on randomized comparisons and does not account for drug costs, cost-effectiveness, patient values, and preferences. Besides, the NCB model only included ischemic stroke and ICH, the most devastating bleeding complication, and did not consider other bleeding events because the severity of other bleeding varied much and is difficult to be ascertained in the registry database. Fifth, the age, CHA$_2$DS$_2$-VASc, and mCHA$_2$DS$_2$-VASc scores of patients were determined using the baseline data at the enrollment and were likely to change during the follow up. However, it is a common limitation that was frequently existent in previous studies. The relationship between the dynamic changes of age and clinical risk scores and the risk of ischemic stroke has not been well investigated before, and it is an important issue that deserves more investigations. In the clinical practice, it is imperative to update the risk scores of AF patients, and the use of OAC should be determined accordingly. Furthermore, the strategies for stroke prevention of each patient could also change during the long-term follow-up. However, the change of treatment could happen for patients within each treatment group, and the accumulative incidence curve of ischemic stroke for the warfarin group was consistently different from that of patients without antithrombotic treatments or under antiplatelet agents during the whole study period, as shown in Figure (A). The pattern of antithrombotic treatments preceding ischemic stroke and ICH was broadly consistent to that used for categorization.
Figure. Cumulative incidence curves for ischemic stroke (A), ICH (B), and ischemic stroke/ICH (C) in different treatment groups. The cumulative incidence curves with log rank tests demonstrates that warfarin was associated with a lower risk of ischemic stroke without an increased risk of ICH among patients with a CHA2DS2-VASc score of 0 (males) or 1 (females), having a mCHA2DS2-VASc score of 1 (males) or 2 (females). AF indicates atrial fibrillation; and ICH, intracranial hemorrhage.
Table 5. The Net Clinical Benefit Analyses for Each Treatment According to Different Weight Models

<table>
<thead>
<tr>
<th>Stroke Prevention Strategy</th>
<th>NCB Based on Different Weight Models, % per Year (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Relative Weight of ICH Compared With Ischemic Stroke According to Singer et al.</td>
</tr>
<tr>
<td>Antiplatelet drugs</td>
<td>–0.26 (–0.47 to –0.67)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>0.63 (0.56–0.69)</td>
</tr>
</tbody>
</table>

Compared with no antithrombotic therapy (reference group)

| Warfarin                   | 0.99 (0.74–1.23) | 1.30 (0.99–1.61) | 1.17 (0.89–1.46) |

CI indicates confidence interval; ICH, intracranial hemorrhage; and NCB, net clinical benefit.

at the enrollment for >80% of the patients. Last, the present study only enrolled Taiwanese Chinese patients, and whether the results can be extrapolated to other populations in Asia remains uncertain. Also, whether our findings are applicable to Asian/Chinese subjects living in Western countries requires further large prospective studies.

Conclusions

In this Asian AF cohort, the mCHA2DS2-VASc score, which assigned 1 point for patients aged 50 to 74 years, performed better than the CHA2DS2-VASc score for stroke risk stratification and would further identify AF patients who may derive a positive NCB from OAC among those with a CHA2DS2-VASc score of 0 (males) or 1 (females).

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Disclosures

Dr Lip reports consultant for Bayer/Janssens, Astellas, Merck, Sanofi, BMS/Pfizer, Biotronik, Medtronic, Portola, Boehringer Ingelheim, Microlife, and Daiichi-Sankyo; speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche, and Daiichi-Sankyo. Dr Wang has received honoraria for continuing medical education lectures from AstraZeneca, Bayer, Boehringer Ingelheim, and Daiichi-Sankyo. The other authors report no conflicts.

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Supplemental Materials

Validation of a Modified CHA2DS2-VASc Score for Stroke Risk Stratification in Asian Patients with Atrial Fibrillation – A Nationwide Cohort Study

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Figure Legends

Supplemental Figure I. Flowchart of study cohort. From year 1996-2006, a total of 224,866 newly-diagnosed AF patients aged ≥ 20 years were identified as the study population. Among the study population, there were 124,271 patients who did not receive any anti-thrombotic therapies, in whom the diagnostic accuracies of CHA₂DS₂-VASc and mCHA₂DS₂-VASc scores were compared. Among 15,948 patients with a CHA₂DS₂-VASc score of 0 (males) or 1 (females), 8,654 patients having a mCHA₂DS₂-VASc score of 1 (males) or 2 (females) due to the resetting of the age threshold were divided into three groups based on the anti-thrombotic strategies, that is, no treatment (n = 6,114), anti-platelet therapy (1,433) and warfarin (1,107). AF = atrial fibrillation; NHIRD = National Health Insurance Research Database.

Supplemental Figure II. ROC curves of CHA₂DS₂-VASc and mCHA₂DS₂-VASc scores in predicting ischemic stroke. The c-indexes based on AUCs for the CHA₂DS₂-VASc and mCHA₂DS₂-VASc scores in predicting ischemic stroke were 0.689 and 0.708, respectively (DeLong test, p value <0.0001). AUC = area under the curve; ROC = receiver operating characteristic.

Supplemental Figure III. A proposed flow chart of stroke prevention using mCHA₂DS₂-VASc score for Asian AF patients. AF patients with a mCHA₂DS₂-VASc score of 0 (males) or 1 (females) were “truly low-risk” and OACs could be clearly omitted. For male patients with a mCHA₂DS₂-VASc score ≥ 1 and female patients with a mCHA₂DS₂-VASc score ≥ 2, OACs should be prescribed and NOACs are the preferred choices. AF = atrial fibrillation; NOACs = non-vitamin K antagonist oral anticoagulants; OACs = oral anticoagulants. Line: solid = best option; dashed = alternative option.
Supplemental Figure I

More than 23 million enrollees

AF patients older than 20 years, \( n = 224,866 \) (124,271 patients without use of any anti-platelet or anticoagulant agent)

AF patients with a CHA₂DS₂-VASc score of 0 (males) or 1 (females)  
\( n = 15,948 \)

Patients aged 50–64 years  
(mCHA₂DS₂-VASc score = 1 for males and 2 for females)  
\( n = 8,654 \)

- No antithrombotic therapy  
  \( n = 6,114 \)
- Anti-platelet drugs  
  \( n = 1,433 \)
- Warfarin  
  \( n = 1,107 \)
Supplemental Figure II

- Sensitivity vs. 1 - Specificity
- P value < 0.0001 between 2 curves

- mCHA₂DS₂-VASc, AUC = 0.708
- CHA₂DS₂-VASc, AUC = 0.689
Supplemental Figure III

Asian AF patients

Stroke risk assessment using mCHA₂DS₂-VASc score

Score 0 (males)
Annual stroke rate = 0.46%

Score 1 (females)
Annual stroke rate = 0.63%

Score ≥ 1 (males)
Annual stroke rate = 3.94%

Score ≥ 2 (females)
Annual stroke rate = 4.34%

Oral anticoagulant

No antithrombotic therapy

NOACs
(rivaroxaban, dabigatran, apixaban, edoxaban)

Well-controlled warfarin