Atrial Fibrillation and the Risk of Ischemic Stroke
Does It Still Matter in Patients With a CHA₂DS₂-VASc Score of 0 or 1?

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Background and Purpose—Atrial fibrillation (AF) is an independent risk factor for stroke. Recent studies have demonstrated that the CHA₂DS₂-VASc scheme is useful for selecting patients who are truly at low risk. The goal of the present study was to compare the risk of ischemic stroke among AF patients with a CHA₂DS₂-VASc score of 0 (male) or 1 (female) with those without AF.

Methods—The study enrolled 509 males (CHA₂DS₂-VASc score 0) and 320 females (CHA₂DS₂-VASc score 1) with AF who did not receive any antithrombotic therapy. Patients were selected from the National Health Insurance Research Database in Taiwan. For each study patient, 10 age-matched and sex-matched subjects without AF and without any comorbidity from the CHA₂DS₂-VASc scheme were selected as controls. The clinical end point was the occurrence of ischemic stroke.

Results—During a follow-up of 57.4±35.7 months, 128 patients (1.4%) experienced ischemic stroke. The event rate did not differ between groups with and without AF for male patients (1.6% vs 1.6%; P=0.920). In contrast, AF was a significant risk factor for ischemic stroke among females (hazard ratio, 7.77), with event rates of 4.4% and 0.7% for female patients with and without AF (P<0.001).

Conclusions—AF males with a CHA₂DS₂-VASc score of 0 were at true low risk for stroke, which was similar to that of non-AF patients. However, AF females with a score of 1 were still at higher risk for ischemic events than non-AF patients. (Stroke. 2012;43:2551-2555.)

Key Words: atrial fibrillation ■ gender ■ oral anticoagulation ■ ischemic stroke

Atrial fibrillation (AF) is the most prevalent sustained cardiac arrhythmia, and its incidence is projected to increase continuously over the next few decades.1 It is an independent risk factor for stroke and is associated with marked morbidity, mortality, and socioeconomic burden.2–4 Although the knowledge about the pathogenesis and treatment of AF has greatly advanced in recent years, stroke prevention with appropriate thromboprophylaxis remains central to AF management. However, there are several limitations and important concerns with regard to the use of oral anticoagulation with warfarin, including a narrow therapeutic window, increased risk of hemorrhage, multiple food and drug interactions, and the need for frequent laboratory monitoring. Consequently, how to identify patients at true low risk for stroke who may not need to use oral anticoagulation is an important issue in managing AF.

Recently, use of the newly developed CHA₂DS₂-VASc scoring system, which extends the CHADS₂ scheme by considering additional stroke risk factors (vascular diseases and female gender), was recommended to guide antithrombotic therapies for AF patients.5,6 Several studies have demonstrated that the new scoring system is useful for selecting “truly low-risk” patients, and that no antithrombotic therapy is necessary for patients with a CHA₂DS₂-VASc score of 0.7–9 However, these previous studies did not enroll patients without AF as a control group. Therefore, the question remains regarding...
whether AF predisposes an individual with a CHA₂DS₂-VASc score of 0 (male) or 1 (female) to ischemic stroke.

The goal of the present study was to compare the risk of ischemic stroke among patients with AF and with a CHA₂DS₂-VASc score of 0 (male) or 1 (female) with patients without AF. We also investigated whether female gender was a risk factor for ischemic stroke in AF patients without other significant comorbidities, as assessed by the CHA₂DS₂-VASc score.

Materials and Methods

Database

This study used the National Health Insurance Research Database 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 residents of Taiwan. The National Health Insurance Research Database is a cohort dataset that contains all of the medical claims data for a random sampling of 1 000,000 beneficiaries from the 25.68 million enrollees in the National Health Insurance program. These random samples have been confirmed by the National Health Research Institutes to be representative of the Taiwanese population. The diagnostic accuracy of the database also has been validated previously. In this cohort dataset, 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 could be followed continuously. The large sample size of this database provided a good opportunity to study the risk of ischemic stroke among AF patients with a low CHA₂DS₂-VASc score (0 or 1).

Study Population

From January 1, 2000 to December 31, 2009, a total of 11,239 adult patients (age 18 years or older) with newly diagnosed AF were identified from the National Health Insurance Research Database. The CHA₂DS₂-VASc score was calculated for each patient on the basis of a point system: 2 points were assigned for a history of stroke or transient ischemic attack or age 75 or older; and 1 point each was assigned for age 65 to 74 years, a history of hypertension, diabetes, recent cardiac failure, vascular disease (myocardial infarction, complex aortic plaque, and peripheral artery disease), and female sex. Thereafter, male patients with a CHA₂DS₂-VASc score of 0 (n=532) and female patients with a CHA₂DS₂-VASc score of 1 (attributable to female gender, n=334) were enrolled. Patients who received antithrombotic therapy with either antiplatelet agents or oral anticoagulation were excluded. Finally, a total of 509 male and 320 female patients were selected as the study group (with AF). For each study patient, 10 age-matched and sex-matched control subjects (without AF) who were not undergoing antiplatelet or anticoagulant therapy and who did not have any risk factor (except for gender) of the CHA₂DS₂-VASc scoring system were selected as the control group. The control patients were identified from the National Health Insurance Research Database during the similar time period as the corresponding study patients were enrolled. The flowchart of the enrollment process is shown in Supplementary Figure I. The clinical end point was defined as the occurrence of ischemic stroke during the follow-up period.

Statistical Analysis

Data are presented as the mean value and standard deviation for normally distributed continuous variables and proportions for categorical variables. Differences between continuous values were assessed with an unpaired 2-tailed t test for normally distributed variables, Mann-Whitney rank-sum test for skewed variables, and χ² testing for nominal variables. The event-free survival curve was plotted via the Kaplan-Meier method with the statistical significance examined by the log-rank test. The risk of ischemic stroke was assessed using the Cox regression analysis. All statistical significances were set at P<0.05 and all statistical analyses were performed SPSS 17.0.

Results

Patient Characteristics

The mean age of the study population was 45.4±12.0 years, and males accounted for 61.4% of patients. The baseline characteristics of patients with and without AF are shown in Table 1. Age, sex, and underlying diseases included in the CHA₂DS₂-VASc scoring system were matched between the study and control groups. With regard to comorbidities other than those included in the CHA₂DS₂-VASc scheme, there were fewer patients with asthma/chronic obstructive pulmonary disease and more with a history of malignancy or liver cirrhosis in the study group than in the control group.

AF and Risk of Stroke in Different Genders

During the follow-up of 57.4±35.7 months, 128 patients (1.4% of the study population) experienced ischemic stroke. AF was a significant risk factor for the occurrence of ischemic events, with a hazard ratio of 2.64 (95% confidence interval, 1.67–4.19; P<0.001) after adjusting for variables with P<0.05 between 2 groups in Table 1 (ie, history of asthma/chronic obstructive pulmonary disease, malignancy, and liver cirrhosis). The Kaplan-Meier curve of freedom from ischemic stroke is shown in Figure 1A. AF patients had a higher event rate than non-AF patients during the follow-up period (2.7% vs 1.3%; P=0.001).

In the subgroup analysis based on genders, AF was a significant risk factor for ischemic stroke for females but not for males (interaction P<0.001). The event rate did not differ between groups with and without AF for males (1.6% vs 1.6%; P=0.920), with an adjusted hazard ratio of 1.27 (95% confidence interval, 0.63–2.61; P=0.535; Table 2). Figure 1B shows the Kaplan-Meier curve of event-free survival between the study and control groups for male

Table 1. Baseline Characteristics of the Patients With and Without Atrial Fibrillation

<table>
<thead>
<tr>
<th>Variables</th>
<th>Study group (With AF)</th>
<th>Control group (Without AF)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>45.4±12.0 (n=829)</td>
<td>45.4±12.0 (n=8290)</td>
<td>1</td>
</tr>
<tr>
<td>Younger than 20</td>
<td>1.3%</td>
<td>1.3%</td>
<td>1</td>
</tr>
<tr>
<td>20 to 40</td>
<td>29.1%</td>
<td>29.1%</td>
<td>1</td>
</tr>
<tr>
<td>40 to 64</td>
<td>69.6%</td>
<td>69.6%</td>
<td>1</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>61.4%</td>
<td>61.4%</td>
<td>1</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>13.5%</td>
<td>13.0%</td>
<td>0.687</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>5.7%</td>
<td>6.9%</td>
<td>0.164</td>
</tr>
<tr>
<td>Asthma/COPD</td>
<td>9.4%</td>
<td>12.2%</td>
<td>0.018</td>
</tr>
<tr>
<td>Malignancy</td>
<td>8.0%</td>
<td>4.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>2.1%</td>
<td>1.2%</td>
<td>0.036</td>
</tr>
<tr>
<td>Autoimmune diseases</td>
<td>4.1%</td>
<td>4.2%</td>
<td>0.882</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; COPD, chronic obstructive pulmonary disease.
patients. In contrast, AF was a significant risk factor for ischemic stroke among females with an adjusted hazard ratio of 7.77 (95% confidence interval, 3.97–15.19; \(P = 0.001\); Table 3).

Females with AF had a higher stroke rate compared with non-AF patients during the follow-up period (4.4% vs 0.7%; \(P = 0.001\); Figure 1C).

Gender and Risk of Ischemic Stroke Among Patients With and Without AF
Among AF patients, females had a higher rate of ischemic stroke than males during the follow-up period (female vs male, 4.4% vs 1.6%; \(P = 0.014\)). The hazard ratio for adverse events among female patients was 2.48 (95% confidence interval, 1.03–5.94; \(P = 0.042\)) after adjusting for coexisting autoimmune diseases, which were more prevalent among females with AF (other variables in Table 1 were not significantly different between male and female patients). In contrast, among non-AF patients, a higher event rate was noted in male compared with female patients (male vs female, 1.6% vs 0.7%; \(P = 0.001\)). Figures 2A and 2B show the

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**Table 2. Risk of Ischemic Stroke in Male Patients (Patients With or Without Atrial Fibrillation)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>All (n=5599)</th>
<th>AF Yes (n=509)</th>
<th>AF No (n=5090)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic stroke, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>91 (1.6)</td>
<td>8 (1.6)†</td>
<td>83 (1.6)</td>
</tr>
<tr>
<td>No</td>
<td>5508 (98.4)</td>
<td>501 (98.4)</td>
<td>5007 (98.4)</td>
</tr>
<tr>
<td>Crude hazard ratio (95% CI)</td>
<td>1.26 (0.61–2.60)</td>
<td>(P = 0.539)</td>
<td></td>
</tr>
<tr>
<td>Adjusted hazard ratio (95% CI)*</td>
<td>1.27 (0.63–2.61)</td>
<td>(P = 0.535)</td>
<td></td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; CI, confidence interval; COPD, chronic obstructive pulmonary disease.

*Adjustment for the variables with \(P < 0.05\) between 2 groups in Table 1, including history of asthma/COPD, malignancy, and liver cirrhosis.

†\(P < 0.001\) in comparison with patients without AF.

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**Table 3. Risk of Ischemic Stroke in Female Patients (Patients With or Without Atrial Fibrillation)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>All (n=3520)</th>
<th>AF Yes (n=320)</th>
<th>AF No (n=3200)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic stroke, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>37 (1.1)</td>
<td>14 (4.4)†</td>
<td>23 (0.7)</td>
</tr>
<tr>
<td>No</td>
<td>3483 (98.9)</td>
<td>306 (95.6)</td>
<td>3177 (99.3)</td>
</tr>
<tr>
<td>Crude hazard ratio (95% CI)</td>
<td>7.30 (3.76–14.19)</td>
<td>(P &lt; 0.001)</td>
<td></td>
</tr>
<tr>
<td>Adjusted hazard ratio (95% CI)*</td>
<td>7.77 (3.97–15.19)</td>
<td>(P &lt; 0.001)</td>
<td></td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; CI, confidence interval; COPD, chronic obstructive pulmonary disease.

*Adjustment for the variables with \(P < 0.05\) between 2 groups in Table 1, including history of asthma/COPD, malignancy, and liver cirrhosis.

†\(P < 0.001\) in comparison with patients without AF.
Kaplan-Meier curves of event-free survival rate between genders for patients with and without AF, respectively.

Discussion

Main Findings
In this study, we compared the risk of ischemic stroke for AF patients with a CHA₂DS₂-VASc score of 0 (male) or 1 (female) with that of patients without AF. The main findings were as follows: (1) The rate of ischemic stroke was low (0.66 per 100 person-years) among AF patients who had a low CHA₂DS₂-VASc score and who did not receive medications for thromboprophylaxis. (2) For AF males with a CHA₂DS₂-VASc score of 0, the risk of ischemic stroke was similar to that of non-AF patients. (3) For female patients with a CHA₂DS₂-VASc score of 1 (attributable to gender), AF was still an important predisposing factor for ischemic stroke. (4) The effect of gender on the risk of ischemic stroke was opposite for AF and non-AF patients.

AF and Risk of Stroke in Patients With a Low CHA₂DS₂-VASc Score
The CHADS₂ score is the most commonly used scheme in stroke risk stratifications for AF patients, although it classifies a large proportion of patients as being at “intermediate risk” and omits several important thromboembolic risk factors. The new scoring system, the CHA₂DS₂-VASc score, has been proposed to complement the CHADS₂ score and categorizes only a small portion of patients into the intermediate risk category. In a recent nationwide cohort study from Denmark, the CHA₂DS₂-VASc score was proven to be superior to the CHADS₂ score in identifying AF patients with at true low risk for thromboembolism. A large validation study was performed in a United Kingdom cohort of 79,884 AF patients who were followed-up for an average of 4 years. Again, subjects at low risk (CHA₂DS₂-VASc score=0) were at true low risk, with an annual stroke rate of <0.5%. However, these studies did not enroll patients without AF as the control group and were not able to provide direct comparisons for the risk of stroke between AF patients with a low CHA₂DS₂-VASc score and non-AF patients. To address this issue, in the present study, we compared the risk of stroke between AF and non-AF patients. Our results provide convincing evidence that AF patients with a CHA₂DS₂-VASc score of 0 are at low risk for ischemic stroke, similar to patients without AF. The observed high event rate in females with AF supports the recommendation that thromboprophylaxis is still necessary for patients who have only 1 risk factor (female gender) of the CHA₂DS₂-VASc scheme.

Gender Differences in the Risk of Ischemic Stroke
Several studies have reported a higher risk of stroke in females with AF than in males. The CHA₂DS₂-VASc scheme also regards female gender as an important risk factor for thromboembolic events and assigns 1 point for AF females. However, patients enrolled in some of these studies were those who received aspirin, aspirin plus fixed low-dose warfarin, or adjusted-dose oral anticoagulation. Because the purpose of the CHA₂DS₂-VASc scheme is to determine the thromboprophylaxis strategy for AF patients, it would be better to determine the components of the scoring system on the basis of studies enrolling AF patients who are not receiving any agent for thromboprophylaxis. In the Atria study, which enrolled a total of 13,559 AF patients without using warfarin, women were at higher risk than men for AF-related thromboembolism. However, when patients were stratified according to the CHADS₂ score, the annual thromboembolism rate was similar between male (0.5%) and female patients (0.6%) with a CHAD₂S score of 0. Consequently, more evidence was necessary to determine whether females with AF with a CHA₂DS₂-VASc score of 1 (attributable to gender) really had a higher risk of stroke compared with males with AF with a CHA₂DS₂-VASc score of 0. Our results showed that females with AF with a CHA₂DS₂-VASc score of 1 had a risk of stroke that was 2.5-times that of AF males with a score of 0. This finding provides a validation for the CHA₂DS₂-VASc scheme of assigning 1 point for female patients who have no significant underlying diseases.

Figure 2. Gender difference in the risk of ischemic stroke in patients with and without atrial fibrillation (AF). In AF patients, females had a higher rate of ischemic stroke than males during the follow-up period (A). In contrast, a higher event rate was noted in male patients in the non-AF group (B).
estingly, the effect of gender on the risk of ischemic stroke was opposite for AF and non-AF patients, which may suggest that women have an intrinsically higher risk of AF-related stroke.

What is the mechanism behind the gender difference in AF-related thromboembolism risk? In a study performed by Conway et al10 that enrolled 162 AF patients and 324 controls, a higher von Willebrand factor level was noted among females with AF, but not among males with AF, when compared with that of non-AF patients. Wang et al10 further demonstrated that females with AF had a higher level of tissue plasminogen activator antigen after adjusting for other clinical factors, including body mass index, blood pressure, and lipid profiles. Therefore, elevated levels of hemostatic factors may predispose females with AF to ischemic events. However, these factors have not been clearly linked to an increased risk of stroke in AF, and further studies are needed to disclose the exact causes of the observed gender difference.

Study Limitations
There were several limitations of the present study. First, the utilized registry database did not contain personal information concerning smoking habits, physical activity, or body mass index. However, this is a common limitation that also has been noted in previous studies using a registered database.7,17 Besides, we have tried to adjust partly for lifestyle factors by including history of cancer and chronic obstructive pulmonary disease in the multivariate Cox regression models. Second, the types of AF (paroxysmal or nonparoxysmal) were not available from the dataset. However, because the stroke risk does not differ between patients with paroxysmal or nonparoxysmal AF,20–21 the AF type may not confound the findings of this study. Last, although our results demonstrated that AF patients with a CHA2DS2-VASc score of 0 had a stroke rate similar to that of patients without AF, whether these patients can still obtain benefits from the use of antithrombotic agents is unknown, and the question can be answered only by a prospective and randomized trial.

Conclusion
In this cohort study, AF patients with a CHA2DS2-VASc score of 0 had a true low risk of ischemic stroke, which was similar to that of patients without AF. In contrast, females with AF with a CHA2DS2-VASc score of 1 had a higher rate of thromboembolism compared with that of non-AF patients. These findings provide some evidence that was lacking before, and further support the usefulness of the CHA2DS2-VASc scheme in determining the optimal strategy for thromboprophylaxis in AF patients with a score of 0 (for males) or 1 (attributable to female gender).

Sources of Funding
This work was supported in part by grants from the National Science Council (NSC98-2410-H-010-003-MY2) and Taipei Veterans General Hospital (V99C1-140, V99A-153, and V100D-002-3).

Disclosures
None.

References
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Stroke. 2012;43:2551-2555; originally published online August 7, 2012;
doi: 10.1161/STROKEAHA.112.667865

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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