Original Contribution

Patients With Ischemic Stroke and Incident Atrial Fibrillation
A Nationwide Cohort Study

Laurent Fauchier, MD; Nicolas Clementy, MD; Christele Pelade, PhD; Cecile Collignon, PharmD; Emmanuelle Nicolle, MD, MSc; Gregory Y.H. Lip, MD

Background and Purpose—A substantial part of ischemic strokes is attributed to atrial fibrillation (AF). We hypothesized that patients with ischemic stroke without prior diagnosed AF were at higher risk of having a subsequent diagnosis of AF, and this was associated with multiple risk factors.

Methods—This French longitudinal cohort study was based on the national database covering hospital care from 2008 to 2012 for the entire population.

Results—Of 65,807 patients with ischemic stroke in 2009, 48,992 did not have AF at baseline. A total of 4828 of these patients were diagnosed as having AF during a follow-up of 15±15 months (incidence rate 7.9 per 100 person-years). By comparison, the yearly rate of new-onset AF for the 826,416 patients with a cardiac hospitalization was 5.9%. CHADS2 (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack) and CHA2DS2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack [doubled], vascular disease, age 65–75 years, and sex category [female]) scores were both associated with the risk of new-onset AF during follow-up (CHADS2: hazard ratio [HR] 1.70, 95% confidence interval [CI] 1.66–1.75; CHA2DS2-VASc: HR 1.45, 95% CI 1.42–1.48). The c statistics were 0.700 (95% CI 0.696–0.706) for CHADS2, and 0.706 (95% CI 0.702–0.710) with CHA2DS2-VASc (P=0.003 for comparison of the 2 scores). Independent predictors of subsequent diagnosis of AF were age 65 to 74 years (HR 2.29, 95% CI 2.06–2.54), age ≥75 years (HR 3.31, 95% CI 3.02–3.64), hypertension (HR 1.22, 95% CI 1.13–1.32), heart failure (HR 2.56, 95% CI 2.41–2.72), and vascular disease (HR 1.10, 95% CI 1.04–1.17).

Conclusion—Ischemic stroke was associated with a substantially increased risk of incident AF, particularly among individuals with higher CHADS2 or CHA2DS2-VASc scores. These risk scores seem to be simple tools for identifying patients at higher risk of incident AF after ischemic stroke. (Stroke. 2015;46:00.00. DOI: 10.1161/STROKEAHA.115.010270.)

Key Words: atrial fibrillation ■ heart failure ■ ischemic stroke ■ risk prediction

Atrial fibrillation (AF) is the most common cardiac rhythm disorder, and its prevalence will at least double in the next 50 years because of an aging population.1 A substantial part of ischemic strokes occurs in patients with AF, and one in 5 of all strokes can be attributed to AF.2 Although ischemic stroke is among the leading causes of death and disability, its cause may, however, remain unexplained even after routine evaluation in 20% to 40% of cases.3,4 Documentation of AF is required to initiate anticoagulant therapy after ischemic stroke.2 Given the often paroxysmal and asymptomatic nature of AF, this arrhythmia may not be detected easily or early with the use of traditional monitoring techniques.5,8 In the absence of documented AF, antiplatelet agents are usually recommended.4 The CHADS2 (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack) and CHA2DS2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack [doubled], vascular disease, age 65–75 years, and sex category [female]) scores have emerged as the dominant prediction tools to estimate the risk of stroke or systemic thromboembolism in patients with AF.9,10 These clinical tools have predictive capacity for adverse outcomes even in patients without known AF, including the risk of death after stroke, the risk of incident AF, and the risk of stroke in unselected patients, in patients with stable coronary artery or after an acute coronary syndrome.11–16

A better identification of the risk of incident AF in patients with ischemic stroke is currently a challenge. We aimed to identify patients with ischemic stroke without prior diagnosed AF who are at higher risk of developing or having a subsequent diagnosis of incident AF based on multiple risk factors.

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We hypothesized that CHADS\textsubscript{2} and CHA\textsubscript{2}DS\textsubscript{2}-VASc scores may be useful tools for this purpose, and we evaluated their respective usefulness for prediction of new (or previously unknown) incident AF in a large unselected population of patients discharged after an ischemic stroke.

Methods

Selection of Patients

This French longitudinal cohort study was based on the national hospitalization database covering hospital care for the entire population. The main outcome measure was rate of incident AF. Data of all the patients admitted with ischemic stroke in France from January 2008 to December 2012 were collected from the national administrative database, the Program de Médicalisation des Systèmes d’Information (PMSI), inspired by the US Medicare system. Since 2004, each hospital’s budget has been linked to the medical activity described in this specific program, which compiles discharge abstracts related to all admissions in the 1546 French healthcare facilities. These data are rendered anonymous, which makes it possible to link discharge abstracts related to a given patient. Routinely collected medical information includes the principal diagnosis, secondary diagnoses, and procedures performed. Diagnoses identified are coded according to the International Classification of Diseases, Tenth Revision. The reliability of PMSI data has already been assessed, and PMSI has previously been used to study patients with stroke, myocardial infarction, and AF.

The study population comprised adults with a diagnosis of acute ischemic stroke (I63 and its subsections using International Classification of Diseases, Tenth Revision codes) coded in the principal diagnosis (ie, the health problem that justified admission to hospital), the related diagnosis (ie, potential chronic disease or health state during hospital stay), or the significantly associated diagnosis (ie, comorbidity or associated complication) who were hospitalized from January 1 to December 31, 2009. Of note, asymptomatic cerebrovascular diseases and sequelae of stroke have different codes (I65-I66 and I69 with subdivisions) to be distinguished from acute strokes in the patients of our analysis. Patient information (demographics, comorbid conditions, medical history, and events during follow-up or during hospitalization) was described using data collected from the hospital records from January 1, 2008, to December 31, 2012. For each hospital stay, all diagnoses were obtained together at discharge. We calculated the CHADS\textsubscript{2} score and CHA\textsubscript{2}DS\textsubscript{2}-VASc score as previously described. In addition, we obtained information for a control group of patients with hospitalization with cardiac condition as a primary diagnosis (eg, I0 to I5 with subdivisions) in France over the same period.

As a retrospective observational analysis from a national database, patient’s informed consent was not obtained. Procedures for data collection and management were approved by the Conseil National de l’Informatique et des Libertés, the independent National ethical committee protecting human rights in France, which ensures that all information is kept confidential and anonymous.

Statistical Analysis

The characteristics of the patients were given as percentages and means±standard deviation. The population of individuals seen with ischemic stroke without prior AF was analyzed by calculating incidence rates of new-onset AF and by multivariable Cox regression models and compared with the population with hospitalization related to a cardiac condition as a first diagnosis. A proportional hazard model was used to identify independent characteristics associated with the occurrence of AF during follow-up. The proportional hazard assumption was checked by plotting the log–log Kaplan–Meier curves. The results were expressed as hazard ratios and 95% confidence intervals. The Harrell’s c statistics with 95% confidence intervals were calculated as a measure of model performance and compared using the DeLong test. A P value <0.05 was considered statistically significant. Statview 5.0 (Abacus, Berkeley, CA) and Medcalc 15.2 (MedCalc Software, Mariakerke, Belgium) were used for statistical analysis.

Results

Of 65,807 patients with ischemic stroke, 48,992 were identified as not having AF at baseline (ie, in their history or during hospital stay with diagnosis of stroke; Figure 1). The baseline characteristics of the study cohort indicated that more than half were aged ≥75 (Table 1). A total of 4828 of these patients were diagnosed as having incident AF during a subsequent hospitalization over a follow-up of 15±15 months. Thus, the total yearly incidence rate for AF for participants with ischemic stroke was 7.88 per 100 person-years. By comparison, the yearly rate of new-onset AF for the 826,416 participants with a cardiac hospitalization on the same period was 5.91%.

CHADS\textsubscript{2} and CHA\textsubscript{2}DS\textsubscript{2}-VASc scores predicted subsequent hospital discharge with a new diagnosis of AF in those patients with ischemic stroke, without preexisting AF at baseline (Table 2 and Figure 2). Multivariable analysis indicated that increasing CHADS\textsubscript{2} and CHA\textsubscript{2}DS\textsubscript{2}-VASc scores were both associated with the risk of new-onset (or previously undiagnosed) incident AF during follow-up (CHADS\textsubscript{2} as a continuous variable: hazard ratio 1.70, 95% confidence interval 1.66–1.75; CHA\textsubscript{2}DS\textsubscript{2}-VASc: hazard ratio 1.45, 95% confidence interval 1.42–1.48). The annual incidence of AF increased in a stepwise fashion and reached 11.1% in patients with CHADS\textsubscript{2} ≥4 and 12.4% in those with CHA\textsubscript{2}DS\textsubscript{2}-VASc ≥6 (Table 3).

Among the risk factors constituting the CHADS\textsubscript{2} and CHA\textsubscript{2}DS\textsubscript{2}-VASc scores, only age 65 to 74 years, age ≥75 years, hypertension, heart failure, and vascular disease were independent predictors of subsequent diagnosis of AF (Table 4).

Each score had a moderate discrimination performance for prediction of incident AF, whereby the c statistics were 0.700

![Figure 1. Flow chart of the study patients.](http://stroke.ahajournals.org/
with CHADS₂ and 0.706 with CHA₂DS₂-VASc (P=0.003 for comparison of the 2 scores).

### Discussion

To our knowledge, this is the largest study to examine the risk of incident AF in a population of non-AF patients after ischemic stroke. Our principal finding is that ischemic stroke was associated with substantially increased risk of AF among individuals with higher CHADS₂ or CHA₂DS₂-VASc scores. Thus, an earlier identification of these patients with ischemic stroke and awareness of the risks of incident AF should be part of the holistic management of such patients.

Risk factors, such as ageing, diabetes mellitus, hypertension, obesity, and cardiovascular disease, including alterations in cardiac structure and function, consistently predispose individuals to AF. However, few tools integrate multiple risk factors to establish an individual’s absolute risk of incident AF after stroke. Establishment of a risk score would help to identify individuals with ischemic stroke at highest risk of having AF, in whom antithrombotic strategy may be different, and to target enrollment in future prevention trials. Thus, we had hypothesized that AF may be predicted by simple risk stratification tools using clinical factors that can be assessed in primary care.

The CHADS₂ and CHA₂DS₂-VASc scores are validated tools to estimate the risk of stroke or systemic thromboembolism in patients with documented AF. The prestroke CHADS₂ score is also associated with neurological or functional outcomes and long-term fatal ischemic heart disease after ischemic stroke in patients with AF. An association between the prestroke CHADS₂ score and long-term mortality after stroke in both patients with and without AF has also been reported. Additionally, the prestroke CHA₂DS₂-VASc score has been linked to long-term mortality, stroke recurrence, and cardiovascular events in ischemic stroke patients without AF. However, previous studies have not evaluated the clinical utility of these scores in estimating the risk of subsequent diagnosis of AF in patients with ischemic stroke, given that this may have major therapeutic implications.

Many components of the CHADS₂ and CHA₂DS₂-VASc scores are associated with higher prevalence of AF. Consistently reported risk indicators of AF in previous studies were sex, advancing age, body mass index, hypertension, heart failure, myocardial infarction, and valvular heart disease. Smoking and diabetes mellitus, though consistently related to incident AF, are less strongly associated with AF than with other CV diseases. Indeed, we actually found that sex and diabetes mellitus were not associated with higher risk of being diagnosed with AF after ischemic stroke after adjustment for other components of the CHA₂DS₂-VASc score. Schnabel et al built a risk-prediction tool for incident AF in the Framingham...
American or European subjects. Asian subjects being somewhat different than that in North study, and the annual incidence of AF was lower (5.9%) than what was markedly lower than those in our study, resulting in a dramatic decrease of AF still deserve confirmation in prospective trials. Our results would suggest that such a strategy for prevention of AF should be more focused on hypertension, heart failure, and vascular disease than on diabetes mellitus.

In addition, higher scores identify patients more likely to develop incident AF, which may be asymptomatic. Such asymptomatic AF may first be diagnosed when the patient presents with a stroke. Therefore, when patients who have a high score and no previously documented AF exhibit acute stroke/transient ischemic attack, we may have to survey for silent AF more aggressively to reduce the risk of recurrent ischemic events through appropriate anticoagulant therapies. Prolonged monitoring of heart rhythm should become part of the standard care of patients with cryptogenic stroke.8,32 A high CHA2DS2-VASc score may potentially benefit from upstream therapies, like statins or renin–angiotensin system blockers, for AF prevention. However, whether the upstream therapy for these patients and better controls of the underlying disease could decrease the incidence of AF still deserve confirmation in prospective trials. Our results would suggest that such a strategy for prevention of AF should be more focused on hypertension, heart failure, and vascular disease than on diabetes mellitus.

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Study Limitations
A main limitation of this study was inherent to its retrospective observational nature. The study methodology possibly underestimated the true incidence of AF in this population and may overestimate the importance of the components of the CHADS2 and CHA2DS2-VASc scores, which might predispose to hospitalization. Whether it indicates any potential for modifying risk of developing AF is still speculative and should be confirmed prospectively. Some personal information, such as smoking
habit, physical activity, and body mass index, was not available from this registry database. Although it would be informative to compare both CHADS2 and CHA2DS2-VASc scores against the Framingham score, the lack of all necessary parameters preclude this possibility. Besides, the echocardiographic parameters were lacking in the present study because they are not available in such a database. However, the goal of the present study was to validate whether simple risk tools were useful in predicting the risk of new-onset AF in patients without obtaining more detailed information or performing further examinations. In view of costs, use of echocardiography to predict risk of AF is unlikely to be justifiable for screening in a large population. The occurrence of incident AF was based on the diagnostic code registered by a responsible physician and was not further checked externally. However, this was a common limitation also noted in most previous studies, and AF diagnoses in outpatients were not included. Finally, arrhythmia monitoring, such as 24-hour Holter monitor or cardiac event recording, was not routinely performed for every patient to detect asymptomatic AF, and it may underestimate the true incidence of new-onset AF.

**Conclusions**

Ischemic stroke was associated with substantially increased risk of AF, particularly among individuals with higher CHADS2 or CHA2DS2-VASc scores. These scores seem to be simple risk tools for identifying patients at higher risk of AF after ischemic stroke among patients without known AF. Strategies aimed at preventing AF early during the course after ischemic stroke or at better diagnosing incident AF in prevention of ischemic stroke are warranted.

### Table 3. Hazard Ratio of New-Onset Atrial Fibrillation in Patients With Ischemic Stroke With Different CHADS2 and CHA2DS2-VASc Scores (in Comparison to the Patients With Score of Two)

<table>
<thead>
<tr>
<th>CHADS2 score</th>
<th>Number of Patients (N=702 502)</th>
<th>Number of New-Onset AF (N=9187)</th>
<th>Hazard Ratio</th>
<th>95 CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 (reference)</td>
<td>8642</td>
<td>209</td>
<td>1</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>3</td>
<td>14817</td>
<td>812</td>
<td>2.12</td>
<td>1.82–2.47</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>4</td>
<td>16295</td>
<td>1751</td>
<td>3.60</td>
<td>3.12–4.16</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>5</td>
<td>7754</td>
<td>1626</td>
<td>6.38</td>
<td>5.52–7.36</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>6</td>
<td>1484</td>
<td>430</td>
<td>8.67</td>
<td>7.35–10.22</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CHA2DS2-VASc score</th>
<th>Number of Patients (N=702 502)</th>
<th>Number of New-Onset AF (N=9187)</th>
<th>Hazard Ratio</th>
<th>95 CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 (reference)</td>
<td>3254</td>
<td>52</td>
<td>1</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>3</td>
<td>6457</td>
<td>170</td>
<td>1.30</td>
<td>0.95–1.77</td>
<td>0.10</td>
</tr>
<tr>
<td>4</td>
<td>7906</td>
<td>380</td>
<td>2.42</td>
<td>1.81–3.23</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>5</td>
<td>11006</td>
<td>866</td>
<td>3.93</td>
<td>2.97–5.20</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>6</td>
<td>11123</td>
<td>1382</td>
<td>5.75</td>
<td>4.36–7.58</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>7</td>
<td>6374</td>
<td>1201</td>
<td>8.14</td>
<td>6.16–10.74</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>8</td>
<td>2408</td>
<td>653</td>
<td>10.83</td>
<td>8.17–14.37</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>9</td>
<td>464</td>
<td>124</td>
<td>10.29</td>
<td>7.44–14.22</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; CHADS2, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack; CHA2DS2-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack (doubled), vascular disease, age 65–75 years, and sex category (female); and CI, confidence interval.

### Table 4. Cox Regression Analysis for Prediction of Atrial Fibrillation After Ischemic Stroke for Items Constituting the CHA2DS2-VASc Score

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Univariate Analysis</th>
<th>P Value</th>
<th>Multivariable Analysis</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td></td>
<td>HR (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Age 65–74 y</td>
<td>0.89 (0.83–0.95)</td>
<td>0.001</td>
<td>2.29 (2.06–2.54)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age ≥75 y</td>
<td>2.54 (2.39–2.70)</td>
<td>&lt;0.0001</td>
<td>3.31 (3.02–3.64)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.20 (1.13–1.27)</td>
<td>&lt;0.0001</td>
<td>1.01 (0.95–1.07)</td>
<td>0.72</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.88 (1.74–2.03)</td>
<td>&lt;0.0001</td>
<td>1.22 (1.13–1.33)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.06 (1.00–1.13)</td>
<td>0.05</td>
<td>0.93 (0.87–0.99)</td>
<td>0.02</td>
</tr>
<tr>
<td>Heart failure</td>
<td>3.15 (2.98–3.33)</td>
<td>&lt;0.0001</td>
<td>2.56 (2.41–2.72)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peripheral vascular disease or</td>
<td>1.46 (1.39–1.55)</td>
<td>&lt;0.0001</td>
<td>1.10 (1.04–1.17)</td>
<td>0.002</td>
</tr>
<tr>
<td>myocardial infarction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CHADS2 indicates congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack; CHA2DS2-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack (doubled), vascular disease, age 65–75 years, and sex category (female); and CI, confidence interval.
Disclosures
Dr Fauchier has served as a consultant for Bayer, Medtronic, and Sanofi Aventis, has received funding for conference travel and educational symposia from Boehringer Ingelheim, Bayer, Medtronic, and Sanofi Aventis, and has received grant research from Bayer. Dr Clemency has received funding for conference travel and educational symposia from Medtronic. Drs Pelade, Collignon, and Nicolle are employees of Medtronic. Dr Lip has served as a consultant for Bayer, Astellas, Merck, AstraZeneca, Sanofi Aventis, Biotronik, BMS/Pfizer, and Boehringer Ingelheim and has been on the speakers bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, and Sanofi Aventis.

References
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Abstract

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表4 CHA2DS2-VAScスコアを構成する項目による虚血性脳卒中後の心房細動発症の予測に対するCox回帰解析

<table>
<thead>
<tr>
<th>共変量</th>
<th>単変量解析</th>
<th>多変量解析</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p値</td>
</tr>
<tr>
<td>年齢65～74歳</td>
<td>0.89 (0.83～0.95)</td>
<td>0.001</td>
</tr>
<tr>
<td>年齢75歳以上</td>
<td>2.54 (2.39～2.70)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>女性</td>
<td>1.20 (1.13～1.27)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>高血圧</td>
<td>1.88 (1.74～2.03)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>糖尿病</td>
<td>1.06 (1.00～1.13)</td>
<td>0.05</td>
</tr>
<tr>
<td>心不全</td>
<td>3.15 (2.98～3.33)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>末梢血管疾患もしくは心筋梗塞</td>
<td>1.46 (1.39～1.55)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

CHA2DS2-VAScスコアを構成する項目：CHADS2：うっ血性心不全、高血圧、年齢≥75歳、糖尿病、脳卒中／一過性脳虚血発作の既往、CHA2DS2-VAScスコア：うっ血性心不全、高血圧、年齢≥75歳、糖尿病、脳卒中／一過性脳虚血発作の既往（2点）、末梢血管疾患、65～75歳、性別（女性）、CI：信頼区間。