Reliable Identification of “Truly Low” Thromboembolic Risk in Patients Initially Diagnosed With “Lone” Atrial Fibrillation
The Belgrade Atrial Fibrillation Study

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Background—The CHA2DS2-VASc (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, previous Stroke/transient ischemic attack [TIA], Vascular disease, Age 65–74 years, and Sex category [female gender]) schema recently has been introduced to complement the CHADS2 (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, and previous stroke or TIA) score and improve the identification of atrial fibrillation (AF) patients at “truly low risk” for thromboembolism. We tested the predictive ability of the CHA2DS2-VASc, CHADS2, and van Walraven risk stratification schemes in a cohort of “lone” AF patients with a 12-year follow-up.

Methods and Results—We conducted a registry-based, observational cohort study of 345 patients initially diagnosed with “lone” AF between 1992 and 2007. At baseline, all patients had the CHADS2 and van Walraven scores of 0, and 262 (75.9%) had a CHA2DS2-VASc score of 0. During follow-up (or within a year prior to stroke), 228 (66.1%), 234 (67.8%), and 150 patients (43.5%) retained the CHADS2, van Walraven, and CHA2DS2-VASc scores of 0, respectively. The overall rate of ischemic stroke was 0.19 (95% CI: 0.18–0.20) per 100 patient years. In the multivariable analysis, only the CHA2DS2-VASc score of 0 was significantly related to the absence of stroke (odds ratio 5.1, 95% CI: 1.5–16.8, P = 0.008). Only the CHA2DS2-VASc score had a significant prediction ability (c-statistic 0.72 [0.61–0.84], P = 0.031).

Conclusions—The CHA2DS2-VASc score reliably identified the “lone” AF patients who were at “truly low risk” for thromboembolism, and was the only tested risk stratification scheme with a significant predictive ability for thromboembolism among lone AF patients. (Circ Arrhythm Electrophysiol. 2012;5:319-326.)

Key Words: atrial fibrillation ■ stroke risk stratification ■ “lone” ■ AF ■ AF-related thromboembolism ■ oral anticoagulation

Atrial fibrillation (AF) is associated with an increased risk of stroke or other thromboembolism, which is strongly influenced by the presence of additional thromboembolic risk factors.1 Oral anticoagulation clearly has been shown to be superior to aspirin or placebo for the reduction of AF-related thromboembolism.2 Given the disadvantages of oral anticoagulation with vitamin K antagonists (eg, warfarin), various thromboembolic risk stratification schemas have been developed to identify “high risk” AF patients who would have a clear benefit from such therapy.1,3,4 However, most of the available schemes artificially classify thromboembolism risk into “low,” “moderate/intermediate,” and “high” risk strata, with variable proportions of patients classified into the same risk category, indicating some inaccuracy in identification of AF patients at high thromboembolic risk.4–7 Indeed, one of the most commonly used schemes, the CHADS2 (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, 1 point each, and previous stroke or transient ischemic attack [TIA], 2 points) score, classifies the largest proportion of AF patients into the intermediate thromboembolic risk category, and has modest predictive value (c-statistic approximately 0.6).8,9 More recently, oral anticoagulants have been established to be superior to aspirin in AF patients at intermediate thromboembolic risk,10–12 and aspirin does not further significantly reduce thromboembolic risk in low risk AF patients.13 Also, the availability of new oral anticoagulants that overcome the limitations of the vitamin K antagonists has changed the paradigm so that greater efforts should

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imimately 0.6).8,9 More recently, oral anticoagulants have been established to be superior to aspirin in AF patients at intermediate thromboembolic risk,10–12 and aspirin does not further significantly reduce thromboembolic risk in low risk AF patients.13 Also, the availability of new oral anticoagulants that overcome the limitations of the vitamin K antagonists has changed the paradigm so that greater efforts should
be made to identify AF patients who are at "truly low risk" for thromboembolism, who are not likely to benefit from antithrombotic therapy, while those with ≥1 stroke risk factors should be considered for oral anticoagulation therapy. Indeed, a recent Markov decision analysis model suggests that with the availability of new, safe oral anticoagulants, such therapy should even be considered in patients at ischemic stroke rates of 0.9%/yr and above.16

Efforts to identify "low risk" patients with AF have been proposed. Van Walraven et al17 suggested the use of a simple clinical prediction rule to identify AF patients at low risk for stroke by excluding previous stroke or TIA, treated or untreated hypertension, angina or previous myocardial infarction, and diabetes mellitus. More recently, to complement the CHADS2 score, a refinement of thromboembolic risk stratification by the inclusion of additional common risk factors has been proposed, the CHA2DS2-VASc (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, previous Stroke/TIA, Vascular disease, Age 65–74 years, and Sex category [female gender]) score, which consistently improves the recognition of "truly low risk" AF patients.9,14,15,18,19

However, the CHA2DS2-VASc score has not been tested in patients with so-called "lone" AF (defined as patients aged ≤60 years with AF and no evidence of associated cardiopulmonary or other disease, including hypertension). In general, lone AF patients are considered to be at low risk of AF complications, including thromboembolism, and currently no thromboprophylaxis (or aspirin) is recommended.15,20

In the present study, we have compared the predictive ability of the 3 risk stratification schemas (CHADS2, CHA2DS2-VASc, and van Walraven) to identify "lone" AF patients free of thromboembolism (that is, "lone" AF patients who were at "truly low" risk for thromboembolism) over a 12-year follow-up period. This was tested in a cohort of carefully characterized patients with first diagnosed "lone" AF in whom we tested the hypothesis that the CHA2DS2-VASc score provided more accurate identification of "truly low risk" patients among patients initially diagnosed as "lone" AF, when compared with the CHADS2 score and van Walraven schemes.

Methods

Patient Selection and Study Design

We conducted an observational study of patients with first diagnosed “lone” AF in the Belgrade Atrial Fibrillation Study, which was a prospectively completed registry of patients with nonvalvar AF seen in the Clinical Centre of Serbia between 1992 and 2007. This is the main cardiology center for specialist arrhythmia services, serving the population of Belgrade and the rest of the country. All patients gave informed consent.

Detailed diagnostic evaluation was performed to confirm the diagnosis of “lone” AF by excluding the acute causes of AF or any underlying comorbid disease. History, physical examination, 12-lead ECG, blood pressure measurement, blood and urine analysis, chest radiography, and transthoracic echocardiography were performed routinely; stress-testing, coronary angiography, and other diagnostic procedures were used if needed.

Cardiac diseases and noncardiac disorders were noted in the presence of a detailed medical record on diagnosis and treatment or a self-reported history of the disease, or when standard diagnostic criteria were fulfilled at baseline diagnostic evaluation. Hypertension was diagnosed if the patient had a physician-confirmed diagnosis and was taking antihypertensive therapy, or with an untreated blood pressure of >150/90 mm Hg. Coronary artery disease was suspected in the presence of chest pain syndrome (typical anginal pain or atypical chest pain) or angina equivalent, and further assessed by echo-stress testing (as needed) and confirmed by coronary angiography (significant coronary artery disease was defined as stenosis of ≥70% in at least 1 major epicardial coronary artery, or ≥50% in the left main coronary artery). Myocardial infarction was diagnosed using standard criteria: typical chest pain, cardiac enzyme abnormalities, and typical ECG abnormalities. Congestive heart failure (CHF) was defined by clinical symptoms (dyspnea and fatigue during exercise or at rest), signs of fluid retention on physical examination (pulmonary congestion or peripheral edema), or pulmonary congestion on chest radiography, followed by a comprehensive echocardiographic examination and other diagnostic procedures (as needed) to clarify the underlying structural or functional cardiac disorder. Valvular disease was diagnosed according to the 2007 guidelines on the valvular heart disease.21 Only patients with normal valvular morphology and function were included in the study, although "trivial," mild valvular regurgitation was allowed.

Following the analysis of detailed medical records for each patient, baseline lone AF was classified to paroxysmal, persistent, or permanent according to the 2006 American College of Cardiology/American Heart Association/European Society of Cardiology Guidelines.22 For the prevention of thromboembolism, aspirin or oral anticoagulants were prescribed according to guideline recommendations that corresponded to the given study period.

Thromboembolic Risk Scores

Based on the van Walraven clinical prediction rule, AF patients were classified into the low thromboembolic risk category in the absence of previous stroke or TIA, treated or untreated hypertension, angina or previous myocardial infarction, and diabetes mellitus.16 The CHADS2 score was calculated by giving 1 point each for congestive heart failure, hypertension, age ≥75 years, and diabetes, and 2 points for prior stroke or TIA,16 and patients with 0 points were classified into the “low risk” category. The CHA2DS2-VASc score was calculated by giving 1 point each for congestive heart failure or left ventricular systolic dysfunction (left ventricular ejection fraction ≤40%), hypertension, diabetes, peripheral vascular disease (including prior myocardial infarction or complex aortic plaque), age 65 to 74 years, and female gender, and 2 points for prior stroke or TIA and for age ≥75 years.15 Again, patients with a CHA2DS2-VASc score of 0 were classified as “low risk.”

Follow-Up and Outcome Parameters

Follow-up lasted ≥5 years or until death. Thromboembolic risk scores were reassessed annually. Ischemic stroke was suspected in the presence of sudden-onset, focal neurological deficit lasting >24 hours, and the diagnosis was confirmed by a neurologist; TIA was defined as a sudden-onset, focal neurological deficit lasting <24 hours as diagnosed by a neurologist (records from neurology wards of local hospitals or neurology clinics also were included as evidence of central embolism). Peripheral thromboembolism was defined as thromboembolic events outside the brain, retina, heart, and lungs.

Statistical Analyses

Following a test of statistical normality, continuous variables are presented as mean±SD. Categorical variables are reported as counts with percentages. Incidence rates of outcome events are presented as linearized rates (percentage rates, rates per 100 patient years of follow-up).

A multivariable logistic regression analysis was used to study the relationship between clinical characteristics, clinical type of AF, and van Walraven, CHADS2, and CHA2DS2-VASc scores of 0 with the use of oral anticoagulation during follow-up (which was the dependent variable in the model). Univariate and multivariable logistic regression analyses also were used to study the relationships between independent variables (van Walraven, CHADS2, and CHA2DS2-
VASc scores of 0 adjusted for the use of oral anticoagulation or aspirin) and outcome parameters (the absence of thromboembolic events was entered as a dependent variable). Independent variables (van Walraven, CHADS2, and CHA2DS2-VASc scores) were defined as categorical variables (that is, score value of 0 or 0). A patient was classified as having a score of 0 only if all his or her score values over the course of follow-up equaled 0. Patients who have experienced stroke during follow-up were classified as having score of 0 only if the score values from baseline to the time of stroke were equal to 0.

The relationships of age, baseline clinical characteristics, clinical type of AF, and development of new structural cardiac diseases during follow-up with the absence of thromboembolic events also were analyzed using a logistic regression method. For patients who have experienced a thromboembolic event during follow-up, new structural cardiac diseases were considered only if documented before the thromboembolic event. The logistic regression method was used given the extremely low risk nature of our population (as would be expected, from a cohort of lone AF patients), resulting in the very small number of strokes (total of 8 events) that were spread over a very long time interval (that is, 7th to 20th year of follow-up).

The c-statistic, a measure of the area under the receiver-operator characteristic (ROC) curve, quantified the predictive validity of the van Walraven, CHADS2, and CHA2DS2-VASc scores, and tested the hypothesis that these schemes performed significantly better than chance (indicated by a c-statistic ≥0.5). The c-statistic quantifies discriminant ability, whereas the odds ratio (OR) quantifies the increased relative “risk” of the absence of thromboembolic events, with van Walraven, CHADS2, and CHA2DS2-VASc scores, respectively. In addition, pairwise comparisons of the ROC curves were performed using the approach of DeLong, DeLong, and Clarke-Pearson.23

A value of P<0.05 was considered statistically significant. Statistical analysis was performed using SPSS 17.0 software package (SPSS Inc.).

Results

Of 3467 consecutive patients with nonvalvular AF, 1058 patients (30.5%) were diagnosed with first diagnosed AF, and 862 of 1058 patients (81.5%) had a structurally normal heart; 32.7% (346 of 1058) patients were aged ≥60 years and had no evidence of underlying cardiopulmonary or other disease, including hypertension (that is, a strict criteria for “lone” AF). Nonetheless, 1 male patient was excluded from further analyses due to possible underlying peripheral vascular disease and an incomplete diagnostic work-up (Figure 1); indeed, the excluded patient subsequently experienced an ischemic stroke at age of 65 years and was not taking oral anticoagulant at the time of stroke.

Of 345 patients with first diagnosed “lone” AF (mean age 43.1±9.9 years, range 18–60), 83 (24.1%) were female. Follow-up was 4166.5 patient years (mean 12.1±7.3 years). Clinical type of AF and thromboprophylaxis at baseline are shown in Table 1. The majority of patients (70%) had paroxysmal AF, and none of the paroxysmal AF patients received oral anticoagulation at the time of stroke.

Table 1. Clinical Features of Lone Atrial Fibrillation Patients at Baseline

<table>
<thead>
<tr>
<th>AF Type</th>
<th>Whole Cohort</th>
<th>No. Antithrombotic Therapy</th>
<th>Aspirin n (%)</th>
<th>OAC n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>345 (100)</td>
<td>169 (49.0)</td>
<td>131 (38.0)</td>
<td>45 (13.0)</td>
</tr>
<tr>
<td>Age (age range)</td>
<td>43.2±9.9 (18–60)</td>
<td>40.6±9.9 (19–60)</td>
<td>45.7±8.6 (18–60)</td>
<td>45.3±11.3 (18–60)</td>
</tr>
<tr>
<td>Male:female</td>
<td>83:262 (24.1:75.9)</td>
<td>46:123 (27.2:72.8)</td>
<td>34:97 (26.0:74.0)</td>
<td>3:42 (6.7:93.3)</td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>63.2±5.7</td>
<td>66.2±5.6</td>
<td>63.7±5.1</td>
<td>61.2±6.5</td>
</tr>
<tr>
<td>Drug therapies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>115 (33.3)</td>
<td>36 (21.3)</td>
<td>71 (54.2)</td>
<td>8 (17.8)</td>
</tr>
<tr>
<td>Verapamil</td>
<td>43 (12.5)</td>
<td>25 (14.7)</td>
<td>18 (13.7)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Dypopyramide</td>
<td>39 (11.3)</td>
<td>14 (8.2)</td>
<td>19 (14.5)</td>
<td>6 (13.3)</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>25 (7.2)</td>
<td>3 (1.7)</td>
<td>4 (3.1)</td>
<td>18 (40.0)</td>
</tr>
<tr>
<td>No drug</td>
<td>93 (27.0)</td>
<td>80 (52.7)</td>
<td>6 (4.6)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Type of AF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxysmal</td>
<td>241 (69.9)</td>
<td>153 (90.5)</td>
<td>88 (67.2)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Persistent</td>
<td>77 (22.3)</td>
<td>13 (7.7)</td>
<td>26 (19.8)</td>
<td>38 (84.4)</td>
</tr>
<tr>
<td>Permanent</td>
<td>27 (7.8)</td>
<td>3 (1.8)</td>
<td>17 (13.0)</td>
<td>7 (15.6)</td>
</tr>
</tbody>
</table>

Values are presented as N (%).

OAC indicates oral anticoagulants (vitamin K antagonists); AF, atrial fibrillation; LV, left ventricle.
Overall, nearly 50% of patients received no thromboprophylaxis, and only 13% of patients were anticoagulated at baseline (predominantly patients with persistent AF awaiting elective cardioversion; Table 1). Subsequently, 53.6% patients (185 of 345) were prescribed intermittent (107 patients, 31.0%) or long-term (78 patients, 22.6%) oral anticoagulation during follow-up. Total time of oral anticoagulation treatment was 508.8 patient years (mean 2.8 ± 3.4 years). The only multivariable predictors of oral anticoagulation use were permanent or persistent AF (odds ratio [OR]: 6.0, 95% CI: 3.0–12.1 and OR: 5.4, 95% CI: 3.2–9.0, respectively; both \(P \leq 0.001\), and not the various stroke risk scores of 0 (all \(P > 0.05\)).

At baseline, the CHADS2 and van Walraven scores equaled 0 in all patients, while baseline CHA2DS2-VASc score was 0 in 262 patients (75.9%), and 83 patients (24.1%) had a CHA2DS2-VASc score of 1 (ie, female patients with “lone” AF). During follow-up, the proportion of patients classified as low thromboembolic risk (scores = 0) gradually decreased with each of the 3 thromboembolic risk schemas (Figure 2). During follow-up (or within a year prior to stroke), 66.1% (228/345) patients remained at low thromboembolic risk according to the CHADS2 score (that is, they retained CHADS2 score = 0), and 67.8% (234/345) of patients still had van Walraven score = 0. Of the 262 patients with baseline CHA2DS2-VASc score of 0, 150 patients (57.3%, or 43.5% of the whole study population) were still in the low-risk category (Table 2A).

**Follow-Up Outcomes**

During follow-up, hypertension was diagnosed in 85 patients (24.6%), myocardial infarction in 6 (1.7%), CHF in 14 (4.1%), and diabetes mellitus in 36 patients (10.4%). In addition, 50 patients (14.5%) were 65 to 74 years old, and 7 patients were ≥75 years old at the end of follow-up (or at the time of stroke).

The overall linearized rate of ischemic stroke was 0.19% (95% CI: 0.18%–0.20%) per 100 patient years (that is, 8 ischemic strokes). The mean time to stroke was 14.1 ± 6.7 years. The earliest occurrence of stroke was at 7th year of follow-up; none of the patients had been taking oral anticoagulant prior to stroke, and there were no recurrent thromboembolic events after the initiation of oral anticoagulation treatment. In addition, half of the patients who experienced ischemic stroke were in the low-risk category according to the van Walraven or CHADS2 scores, and none had a CHA2DS2-VASc score of 0. The rates of thromboembolic events in CHADS2, CHA2DS2-VASc, and van Walraven low-risk categories of patients are shown in Table 2B. There were no peripheral thromboembolic events during follow-up.

**Univariate and Multivariable Analyses**

In the univariate logistic regression analyses, a low risk category in each of the 3 schemas was significantly related to the absence of thromboembolic events during follow-up (all \(P < 0.05\); Table 3). In the multivariable analysis (model with CHADS2, CHA2DS2-VASc, and van Walraven scores of 0, and adjusting for oral anticoagulation or aspirin at any point of the follow-up), only the CHA2DS2-VASc score was related significantly to the absence of thromboembolic events (\(P = 0.008\)). In addition, only the CHA2DS2-VASc score had a significant c-statistic for the absence of thromboembolic events (0.72 [0.61–0.84], \(P = 0.031\); Table 3; Figure 3).

Given the low number of end points (as expected from a lone AF cohort), the comparison of ROC curves for the 3 scores showed no statistically significant differences (all...
Table 2A. The Proportion of Patients With Low Thromboembolic Risk According to CHADS<sub>2</sub>, CHA<sub>2</sub>DS<sub>2</sub>-VASc, and van Walraven Scoring Systems, at Baseline and at the End of Follow-Up

<table>
<thead>
<tr>
<th>Thromboembolic Risk Score</th>
<th>At Baseline</th>
<th>At the End of Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>% of 345</td>
</tr>
<tr>
<td>WHO 2</td>
<td>345</td>
<td>100</td>
</tr>
<tr>
<td>CHA2DS2-VASc</td>
<td>262</td>
<td>75.9</td>
</tr>
<tr>
<td>van Walraven</td>
<td>345</td>
<td>100</td>
</tr>
</tbody>
</table>

P > 0.05, but the greatest difference between areas was found when CHA2DS2-VASc and CHADS2 scores were compared (Table 3).

Logistic regression analyses of the relationship of age, clinical characteristics, and clinical types of AF with ischemic stroke also were performed with the absence of ischemic stroke being the dependent variable. In the univariate analyses, age and the development of any structural cardiac disease were significantly related to the absence of ischemic stroke (OR 0.5, 95% CI: 0.1–0.9 and OR 0.2, 95% CI: 0.03–0.8, respectively, both P < 0.05). In the multivariable analysis (again adjusted for clinical type of AF and the use of oral anticoagulation or aspirin during follow-up), any new structural cardiac disease was significantly inversely related to the absence of ischemic stroke (OR 0.2, 95% CI: 0.03–0.8, P = 0.032).

Discussion

This is the first study to investigate the value of CHA2DS2-VASc and van Walraven scores for identification of those at truly low risk for thromboembolism in patients with “lone” AF, who generally are considered to be at low risk for thromboembolism and other AF-related complications.15,20,25 In the present study, a CHA2DS2-VASc score of 0 had the best predictive value for the absence of ischemic stroke in “lone” AF patients, as compared with CHADS2 and van Walraven scores of 0. Indeed, this is the largest validation of these scores in a prospective cohort of patients with first-diagnosed “lone” AF, with the diagnostic criteria for “lone” AF being strictly applied.22,26

A low annual rate of thromboembolism (≤1%) has been reported consistently in “lone” AF studies.22,24–27 Similar to these findings, the rate of ischemic stroke in the present study was only 0.19 per 100 patient years (<0.2% annually). Indeed, recent practice guidelines for the management of patients with AF recommend the use of aspirin (or even no thromboprophylaxis) in AF patients with low thromboembolic risk.15,20,27 However, “lone” AF patients are not completely devoid of ischemic stroke risk if they are defined by a CHADS2 score of 0. Indeed, we have previously reported that the CHADS2 score may not be particularly useful in stroke risk stratification of patients with “lone” AF, either at baseline or at the time of stroke.25 Moreover, the “classical” CHADS2 score classifies the largest proportion of patients into the intermediate thromboembolic risk category, irrespective of the examined AF cohort.8,9,10

Thus, greater efforts should be made to identify AF patients with the “truly low risk” who would need no antithrombotic therapy at all, while all other AF patients with 1 or more stroke risk factors should be considered for oral anticoagulation. As a step forward to a more comprehensive stroke risk assessment of AF patients with CHADS2 score of 0 (or 1), the CHA2DS2-VASc score has been proposed to complement the CHADS2 score by including the additional common stroke risk factors, and has been recommended in recent guidelines.15

Previous validation studies have demonstrated that stroke risk stratification schemas have only modest predictive value for identification of high stroke risk in AF patients, with c-statistics ranging from 0.60 to 0.70.5,7,14,18,19,29 In the present study, we have examined a discriminant ability of the 3 stroke risk schemas for the identification of those at truly low risk (defined as the absence of ischemic stroke) in a cohort of patients with “lone” AF. Although there was still modest predictive value (c-statistic 0.72), the CHA2DS2-VASc score of 0 was far better than the CHADS2 and van Walraven scores of 0, in the identification of AF patients who are truly low risk for stroke and thromboembolism.

In our study of “lone” AF patients, the development of any structural heart disease was a risk factor for ischemic stroke during follow-up, thus emphasizing the need for a more comprehensive stroke risk stratification of patients with baseline “lone” AF and, presumably, low stroke risk. We also demonstrate that the proportion of those at truly low risk does not remain constant, and decreases continuously over time, especially when using the CHA2DS2-VASc score. Indeed, the more risk factors that are taken into account, the steeper the curve of increase of an actual stroke risk. Therefore, the stroke risk of an individual AF patient should be reassessed regularly (probably at least annually) even if the baseline stroke risk was initially truly low.

In contrast to a previously reported study of 76 “lone” AF patients and 25-year follow-up, wherein the occurrence of ischemic stroke was observed only in patients who gained at
least 1 of the “traditional” stroke risk factors during follow-up (that is, CHF, hypertension, age >75 years, diabetes mellitus, or previous stroke/TIA),24 half of the patients who experienced ischemic stroke in the present study did not have any of the “traditional” risk factors at the time of stroke, and the development of any structural cardiac disease, including myocardial infarction during follow-up, was the only independent predictor of subsequent ischemic stroke in our study. Indeed, prior myocardial infarction has been documented to be an independent predictor of stroke and other thromboembolic events in AF patients30,31 and is incorporated into the CHA2DS2-VASc score (“V” for vascular disease, including peripheral vascular disease, including myocardial infarction and complex aortic plaque).14 In addition, age was also a risk factor for ischemic stroke in our study, consistent with the suggestion that age is not a categorical risk variable (yes/no) starting from 75th year of life, but rather a continuous stroke risk factor.9,15

Study Limitations
The present study is limited by a single center, registry-based observational setting, but it investigates a “real world” and relatively contemporary population of AF patients with “lone” AF with a long follow-up. Nevertheless, the results should be interpreted with some caution because of the small number of ischemic strokes, which is perhaps expected given the generally low stroke risk in carefully defined “lone” AF patients. In addition, oral anticoagulation (and, to a lesser

![Figure 3](http://circ.ahajournals.org/doi/abs/10.1161/CIR.0b013e318220f448)

Figure 3. Receiver-operator characteristic analyses of the CHADS2, CHA2DS2-VASc, and van Walraven scores predictive ability for the absence of ischemic strokes. For c-statistics see Table 3. Only the CHA2DS2-VASc score had a significant c-statistic for the absence of thromboembolic events (0.72 [0.61–0.84], P=0.031). CHADS2 score: C indicates congestive heart failure; H, hypertension; A, age >75 years; D, diabetes mellitus; S2, prior stroke/transient ischemic attack; CHA2DS2-VASc score: C indicates congestive heart failure/left ventricular systolic dysfunction; H, hypertension; A2, age ≥75 years; D, diabetes mellitus; S2, prior stroke/transient ischemic attack; V, vascular disease (peripheral vascular disease, including myocardial infarction and complex aortic plaque); A, age 65–74 years; Sc, sex category (female gender); van Walraven score: the presence or absence of previous stroke or transient ischemic attack, treated or untreated hypertension, angina or previous myocardial infarction, and diabetes mellitus. ROC, receiver-operator characteristic; OR, odds ratio.

Table 3. Univariate and Multivariable Relationships of the CHADS2, CHA2DS2-VASc, and van Walraven Scores of 0 With the Absence of Ischemic Strokes During Follow-Up, and Predictive Ability of Each of the Scores, With Pairwise Comparison of the ROC Curves

<table>
<thead>
<tr>
<th>Risk Score of 0</th>
<th>Univariate Analyses</th>
<th>Predictive Ability of the Score 0</th>
<th>Multivariable Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR 95% CI</td>
<td>P</td>
<td>C-statistic 95% CI</td>
</tr>
<tr>
<td>CHADS2</td>
<td>3.3 1.0–10.2</td>
<td>0.042</td>
<td>0.58 0.38–0.79</td>
</tr>
<tr>
<td>CHA2DS2-VASc</td>
<td>5.1 1.5–16.8</td>
<td>0.008</td>
<td>0.72 0.61–0.84</td>
</tr>
<tr>
<td>van Walraven</td>
<td>9.8 1.2–76.0</td>
<td>0.029</td>
<td>0.65 0.46–0.85</td>
</tr>
</tbody>
</table>

Pairwise Comparison of ROC Curves

<table>
<thead>
<tr>
<th>Difference Between Areas</th>
<th>95% CI</th>
<th>Z-Statistic</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHA2DS2-VASc score vs CHADS2 score</td>
<td>0.1400</td>
<td>−0.0662–0.317</td>
<td>1.332</td>
</tr>
<tr>
<td>CHA2DS2-VASc score vs van Walraven score</td>
<td>0.0673</td>
<td>−0.129–0.264</td>
<td>0.671</td>
</tr>
<tr>
<td>CHADS2 score vs van Walraven score</td>
<td>0.0729</td>
<td>−0.0994–0.245</td>
<td>0.829</td>
</tr>
</tbody>
</table>

CHADS2 score: C indicates congestive heart failure; H, hypertension; A, age >75 years; D, diabetes mellitus; S2, prior stroke/transient ischemic attack; CHA2DS2-VASc score: C indicates congestive heart failure/left ventricular systolic dysfunction; H, hypertension; A2, age ≥75 years; D, diabetes mellitus; S2, prior stroke/transient ischemic attack; V, vascular disease (peripheral vascular disease, including myocardial infarction and complex aortic plaque); A, age 65–74 years; Sc, sex category (female gender); van Walraven score: the presence or absence of previous stroke or transient ischemic attack, treated or untreated hypertension, angina or previous myocardial infarction, and diabetes mellitus. ROC, receiver-operator characteristic; OR, odds ratio.
extent, aspirin) could influence the rate of ischemic stroke during follow-up. However, less than one-fourth of the study population was assigned to a long-term oral anticoagulation (either at baseline or during the follow-up), and all analyses were adjusted for the use of oral anticoagulation or aspirin on multivariable analyses.

**Conclusion**

In conclusion, the CHA$_2$DS$_2$-VASc score of 0 was the most accurate in recognition of “lone” AF patients with a “truly low” risk of thromboembolic complications, compared with the CHADS$_2$ and van Walraven scores of 0. However, due to a dynamic nature of the stroke risk factors, thromboembolic risk of an individual AF patient must be regularly reassessed during the follow-up, even if the baseline stroke risk was “truly low.”

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**Disclosures**

Professor Lip has served as a consultant for Bayer, Astellas, Merck, AstraZeneca, Sanofi, BMS/Pfizer, Biotronik, Portola, and Boehringer-Ingelheim, and has been on the speakers bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, and Sanofi-Aventis.

**References**

CLINICAL PERSPECTIVE

The CHA₂DS₂-VASc schema has recently been introduced to complement the CHADS₂ score and improve the identification of atrial fibrillation (AF) patients at “truly low risk” for thromboembolism. In the present study, we have compared the predictive ability of the 3 risk stratification schemas (CHADS₂, CHA₂DS₂-VASc, and van Walraven) to identify “lone” AF patients free of thromboembolism (that is, “lone” AF patients who were at “truly low” risk for thromboembolism) over a 12-year follow-up period. We found that a CHA₂DS₂-VASc score of 0 had the best predictive value for the absence of ischemic stroke in “lone” AF patients, as compared to CHADS₂ and van Walraven scores of 0. Indeed, this is the largest validation of these scores in a prospective cohort of patients with first-diagnosed “lone” AF, with the diagnostic criteria for “lone” AF being applied strictly. In conclusion, the CHA₂DS₂-VASc score reliably identified the “lone” AF patients who were at “truly low risk” for thromboembolism, and it was the only tested risk stratification scheme with a significant predictive ability for thromboembolism among lone AF patients.
Reliable Identification of "Truly Low" Thromboembolic Risk in Patients Initially Diagnosed With "Lone" Atrial Fibrillation: The Belgrade Atrial Fibrillation Study
Tatjana S. Potpara, Marija M. Polovina, Marina M. Licina, Jelena M. Marinkovic, Milica S. Prostran and Gregory Y.H. Lip

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