Can Patients at Elevated Risk of Stroke Treated With Anticoagulants Be Further Risk Stratified?

Lawrence Baruch, MD; Brian F. Gage, MD; Jay Horrow, MD; Steen Juul-Möller, MD; Arthur Labovitz, MD; Maria Persson, MS; Miguel Zabalgoitia, MD

Background and Purpose—Patients with atrial fibrillation have a varied risk of stroke, depending on age and comorbid conditions. The objective of this study was to assess the predictive value of stroke risk classification schemes and to identify patients with atrial fibrillation who are at substantial risk of stroke despite optimal anticoagulant therapy.

Methods—Seven recognized classification schemes—the American College of Chest Physicians 2001, American College of Chest Physicians 2004, Stroke Prevention in Atrial Fibrillation (SPAF), Atrial Fibrillation Investigators, Framingham, van Walraven, and CHADS2—were compared for their ability to predict ischemic stroke in patients receiving anticoagulant therapy. Data came from the Stroke Prevention using an ORal Thrombin Inhibitor in atrial Fibrillation III and V trials, which compared the efficacy of adjusted-dose warfarin and the direct thrombin inhibitor ximelagatran (36 mg twice daily) in preventing thromboembolic events in 7329 patients with chronic or paroxysmal nonvalvular atrial fibrillation who were at moderate or high risk of ischemic stroke. The main outcome measure was ischemic stroke, as determined by a central event adjudication committee.

Results—During 11 245 patient-years of follow-up, 159 patients had an ischemic stroke (1.4%/year). As indicated by c statistics and hazard ratios, 3 of the classification schemes predicted stroke significantly better than chance: Framingham (c=0.64), CHADS2 (c=0.65), and SPAF (c=0.61).

Conclusions—In a large cohort of atrial fibrillation patients at moderate or high risk of ischemic stroke treated with warfarin or ximelagatan, the CHADS2, SPAF, and Framingham schemes had greater predictive accuracy than chance. This predictive ability may allow clinicians to target high-risk patients for more aggressive intervention. (Stroke. 2007; 38:2459-2463.)

Key Words: anticoagulation ■ atrial fibrillation ■ direct thrombin inhibitors ■ risk prediction ■ stroke

Atrial fibrillation (AF), the most common cardiac arrhythmia, affects >2 million individuals in the United States. Much of AF-related morbidity resides in the 5- to 6-fold increased risk of ischemic stroke. Although anticoagulant and antiplatelet therapies reduce the incidence of stroke in AF patients, the risks of both stroke and bleeding vary. Accordingly, several schemes exist to risk-stratify the nonvalvular AF population to help select appropriate candidates for anticoagulant therapy. Existing risk stratification schemes use age and comorbid conditions, such as prior ischemic stroke, diabetes, heart failure, and hypertension, to classify patients as being at low, moderate, or high thromboembolic risk. Risk classification guides therapy with aspirin or warfarin. The American College of Chest Physicians (ACCP) at its Consensus Conference on Antithrombotic Therapy has promulgated the most recognized schemes. Other accepted schemes include the AF Investigators (AFI), Stroke Prevention in Atrial Fibrillation (SPAF), Framingham, and van Walraven. The stratification schemes vary in estimated stroke risk assigned to individual patients and perhaps in predictive ability.

The risk-stratification schemes arose from studies of patients not receiving anticoagulant therapy. Their predictive abilities in patients receiving anticoagulant therapy are unknown. In the Stroke Prevention using an ORal Thrombin Inhibitor in atrial Fibrillation (SPORTIF) III and SPORTIF V trials, all patients received anticoagulation. The trials compared the efficacy of warfarin with that of the oral direct thrombin inhibitor ximelagatan in preventing thromboembolic events in patients with nonvalvular AF at moderate or high risk of stroke. This substudy of the SPORTIF trials has compared the abilities of 7 recognized classification schemes—ACCP, AFI, SPAF, Framingham, and van Walraven—to risk-stratify patients and predict ischemic stroke in the anticoagulated SPORTIF participants. We hypothesized that the different classification schemes would vary in their predictive ability and their stratification of stroke risk.
Subjects and Methods

Study Population
The rationale, design, and results of SPORTIF III and SPORTIF V have already been published.13–15 These randomized, multicenter, parallel-group trials compared fixed-dose oral ximelagatran with adjusted-dose warfarin for prevention of stroke and systemic embolism in nonvalvular chronic or paroxysmal AF patients at high risk of stroke based on the ACCP 2001 AF guideline recommendations.6

Every participant provided written, informed consent according to a protocol approved by local ethics committees and in accordance with the Declaration of Helsinki. Participants randomly received either fixed-dose ximelagatran, 36 mg twice daily, or dose-adjusted warfarin to maintain the international normalized ratio between 2.0 and 3.0. A masked, interactive, voice-response system allocated treatment according to an adaptive algorithm balanced by country, concomitant aspirin treatment at entry, and history of stroke or transient ischemic attack. Anticoagulants were administered open-label in SPORTIF III15 and double-blinded in SPORTIF V.13

Ascertainment of Outcomes
Periodic administration of a standard stroke-symptom questionnaire enhanced event detection; positive responses prompted additional evaluation. Local study-affiliated neurologists or stroke specialists, masked to treatment, assessed all possible primary events based on clinical findings and results of computed tomography or magnetic resonance imaging of the brain. A single, independent, masked central event adjudication committee reviewed the reports.

Classification Schemes
The SPAF,6 ACCP (2001, 2004),9 van Walraven,10 and AFI11 schemes estimate risk based on the presence of the following various factors, alone or in combination: age, female sex, diabetes, previous stroke or transient ischemic attack, hypertension or elevated systolic blood pressure, coronary artery disease, and left ventricular dysfunction. The Framingham scheme assigns point values to each of the following risk factors: age, gender, systolic blood pressure, diabetes, and prior stroke or transient ischemic attack.11 CHADS2 assigns 1 point each for congestive heart failure, hypertension, age ≥75 years, and diabetes mellitus, with 2 points for a history of stroke or transient ischemic attack.7 The greater the number of CHADS2 or Framingham points, the greater the stroke risk.

Statistical Analyses
With the combined SPORTIF III and SPORTIF V data sets, the primary analysis for this substudy compared the predictive accuracy of 7 classification schemes for the first occurrence of ischemic stroke. Secondary analyses assessed the predictive accuracy of the schemes for all strokes (ischemic and hemorrhagic) and separately for the composite of ischemic stroke and systemic embolic events. The intention-to-treat analyses included all randomized participants, even with incomplete follow-up and exposure truncated at the time of study withdrawal. For CHADS2 and Framingham schemes, a Cox proportional-hazards model (SAS version 8.2; SAS Institute Inc, Cary, NC) calculated stroke rates and quantified the hazard rate for stroke for each 1-point increase in score.

Time-to-event analyses determined the predictive validity of each of the classification schemes. The c statistic, a measure of the area under the receiver operating characteristic curve, quantified the predictive validity of the classification schemes and tested the hypothesis that these classification schemes performed significantly better than chance (indicated by a c statistic of 0.5).16,17 The c statistic quantifies discriminant ability, whereas the hazard ratio quantifies the increased relative risk of stroke across risk strata. The 95% CIs were calculated according to the Poisson approximation.18

To compare the CHADS2 classification scheme, which is based on point scores (0 to 6), with the schemes that categorize patients as being at low, medium or high risk, we also analyzed the predictive value of the CHADS2 scoring system after collapsing CHADS2 into 3 strata: low risk (CHADS2 0), moderate risk (CHADS2 1 to 2), and high risk (CHADS2 3 to 6). Likewise, collapsing Framingham scores of 0 to 7 as low-risk, 8 to 13 as moderate-risk, and 14 to 31 as high-risk strata permitted comparison of Framingham scores to other scoring systems.

Results
The baseline characteristics of the 7329 participants have been previously reported.14 The most common risk factors were hypertension, age, coronary artery disease, and left ventricular dysfunction (Table 1). The percentage of participants in the low-, moderate-, and high-risk cohorts varied, based on the specific risk stratification scheme used (the Figure). Because SPORTIF study-inclusion criteria required high-risk patients by ACCP 2001 criteria,6 few SPORTIF participants were classified as low risk according to the ACCP (2001, 2004), AFI, or CHADS2 classification schemes. Most participants were at high risk by ACCP 2001 (96%), ACCP 2004 (97.5%), van Walraven (99.2%), and AFI (85.1%) schemes.

In contrast, the Framingham scheme, with the ad hoc threshold of ≥14 points, characterized the fewest participants (21.2%) as being at high risk (Table 2). The Framingham and SPAF schemes classified a number of SPORTIF participants as being at low risk. CHADS2 characterized the largest cohort of SPORTIF participants as being at intermediate risk, whereas SPAF classified almost equal numbers of participants as being at moderate and high risk.

During the 11 245 patient-years of follow-up (mean, 1.5 years/patient), 159 participants had an ischemic stroke (1.4 per 100 patient-years; Table 2). The highest stroke rate occurred in patients identified as being at high risk by the Framingham scheme (Tables 2 and 3). All schemes, other than van Walraven’s, which explicitly combines moderate- and high-risk patients, distinguished between moderate- and high-risk subjects. Only the Framingham and CHADS2 schemes distinguished low- from moderate-risk SPORTIF participants (Tables 2 and 3). No strokes occurred in the 238 patient-years categorized as low risk in CHADS2 and the smaller low-risk cohorts defined by the van Walraven (85 patient-years) and ACCP (29 patient-years) schemes.

The SPAF, Framingham, and CHADS2 c statistics had greater predictive accuracy for ischemic stroke than chance (Table 4). When Framingham and CHADS2 classification

| TABLE 1. Distribution of Stroke Risk Factors in SPORTIF III and SPORTIF V Trials (N=7329) |
|--------------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| Risk Factor              | Patients, No. (%)   |
|--------------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| Previous systemic embolic event | 328 (4)            | Age ≥65 y with coronary artery disease | 2764 (38)          |
| Age ≥65 y with diabetes mellitus | 1340 (18)        | Age ≥75             | 2604 (38)          |
| Diabetes                 | 1725 (24)           | Coronary artery disease | 3729 (45)          |
| Previous stroke or transient ischemic attack | 1539 (21)        | Hypertension        | 5625 (75)          |
| Left ventricular dysfunction | 2681 (37)         | Recent heart failure | 110 (2)            |
schemes were collapsed into 3 strata—low, moderate, and high—they maintained their predictive values, with c statistics of 0.61 and 0.64, respectively. CHADS\textsubscript{2} had numerically the highest hazard ratio per increase in risk (Table 4).

Before schema collapse, the hazard ratio was 1.48 (1.31 to 1.66) for CHADS\textsubscript{2}, indicating a 48% increase in ischemic stroke rate per CHADS\textsubscript{2} point ($P<0.0001$), and 1.10 (1.07 to 1.13) for Framingham, indicating a 10% increase per Framingham point ($P<0.0001$). This 5-fold effect ratio reflects the 5-fold greater scale for the Framingham (31-point system) compared with the CHADS\textsubscript{2} (6-point system; Table 3) scheme.

The secondary analyses for the outcome of all strokes (ischemic and hemorrhagic; $n=74$ patients) and for the outcome combining ischemic stroke and systemic embolic events ($n=169$ patients) yielded results similar to those for ischemic stroke alone. Likewise, treatment with either war-

TABLE 2. Years of Follow-Up and Ischemic Stroke Rate Based on Baseline Level of Risk According to the Risk-Stratification Schemes

<table>
<thead>
<tr>
<th>Stratification Scheme</th>
<th>Ischemic Stroke Events/Patient-Years, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low Risk</td>
</tr>
<tr>
<td>ACCP 2001</td>
<td>2/173</td>
</tr>
<tr>
<td></td>
<td>1.2% (0.3–4.6)</td>
</tr>
<tr>
<td>ACCP 2004</td>
<td>0/29</td>
</tr>
<tr>
<td></td>
<td>0% (0–11)</td>
</tr>
<tr>
<td>AFI</td>
<td>2/286</td>
</tr>
<tr>
<td></td>
<td>0.7% (0.2–2.8)</td>
</tr>
<tr>
<td>SPAF</td>
<td>10/1352</td>
</tr>
<tr>
<td></td>
<td>0.7% (0.4–1.4)</td>
</tr>
<tr>
<td>CHADS\textsubscript{2}</td>
<td>0/238</td>
</tr>
<tr>
<td></td>
<td>0% (0–1.3)</td>
</tr>
<tr>
<td>Framingham</td>
<td>32/4552</td>
</tr>
<tr>
<td></td>
<td>0.7% (0.5–1.0)</td>
</tr>
<tr>
<td>van Walraven†</td>
<td>0/85</td>
</tr>
<tr>
<td></td>
<td>0% (0–3.5)</td>
</tr>
</tbody>
</table>

*When calculating the hazard ratio, patients with 0–7 Framingham points or 0 CHADS\textsubscript{2} points were classified as being at low risk; those with 8–13 Framingham points or 1–2 CHADS\textsubscript{2} points were classified as being at moderate risk; and those with ≥13 Framingham points or ≥2 CHADS\textsubscript{2} points were classified as being at high risk.

†van Walraven categorizes patients into low- and elevated-risk subgroups only.

Note: SPORIF entry criteria specified ACCP 2001 classification of high risk.

Percentage of patients classified as being at low, moderate, and high risk, based on the individual risk stratification schemes.

TABLE 3. Years of Follow-Up and Ischemic Stroke Rate Based on CHADS\textsubscript{2} Score and the 5 Framingham Score Cohorts*

<table>
<thead>
<tr>
<th>CHADS\textsubscript{2} Score</th>
<th>Events/Patient-Years, %</th>
<th>Framingham Score</th>
<th>Events/Patient-Years, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0/238</td>
<td>0% (0.0–1.6)</td>
<td>0/238</td>
</tr>
<tr>
<td>1</td>
<td>23/3568</td>
<td>0.6% (0.4–1.0)</td>
<td>49/3718</td>
</tr>
<tr>
<td>2</td>
<td>49/3718</td>
<td>1.8% (1.3–2.5)</td>
<td>39/2150</td>
</tr>
<tr>
<td>3</td>
<td>39/2150</td>
<td>1.8% (1.3–2.5)</td>
<td>71/1111</td>
</tr>
<tr>
<td>4</td>
<td>37/1111</td>
<td>2.4% (1.4–4.6)</td>
<td>13/390</td>
</tr>
<tr>
<td>5</td>
<td>9/380</td>
<td>2.4% (1.1–4.5)</td>
<td>26/31</td>
</tr>
<tr>
<td>6</td>
<td>2/80</td>
<td>2.5% (0.4–8.8)</td>
<td>1/18</td>
</tr>
</tbody>
</table>

*To allow for comparison of stroke risk between the 2 schemes, Framingham scores were collapsed into 5 cohorts, because Framingham scores range from 0–31 whereas CHADS\textsubscript{2} scores range from 0–6. Framingham scores of 0–7 were aligned with a CHADS\textsubscript{2} score of 1 (as opposed to 0) to provide a frame of reference for comparison based on the sample sizes of the respective risk scores. Framingham scores of 0–7 were used to maintain consistency with the remainder of the article. Framingham scores of 26–31 were compared with CHADS\textsubscript{2} scores of 5 and 6 because the stroke rate was almost identical in these 2 CHADS\textsubscript{2} groups, and there were few patients with a CHADS\textsubscript{2} score of 6.
The schemes differed significantly in classifying individual participant’s stroke risks. Many subjects classified as being at moderate or high risk by ACCP 2001, ACCP 2004, van Walraven, or AFI schemes were classified as being at low risk by Framingham and SPAF schemes. A number of patients classified as being at moderate risk according to the CHADS<sup>2</sup> scheme were classified as being at high risk according to ACCP 2001, ACCP 2004, van Walraven, and AFI schemes and at low risk according to Framingham and SPAF schemes. The lowest stroke rates occurred in low-risk patients identified by the CHADS<sup>2</sup>, van Walraven, and ACCP 2004 schemes. However, for the van Walraven and ACCP 2004 schemes, the 95% CIs were wide.

Because many clinicians will consider newer strategies in “high-risk” patients, differences in stroke prediction may affect therapy. For example, dual antithrombotic therapy with warfarin and aspirin is recommended for patients with mechanical heart valves and may prevent ischemic events in selected high-risk patients with AF. Likewise, high-risk patients with AF may benefit from reducing, rather than holding, warfarin therapy before elective procedures. Like- wise, they may more vigorously avoid subtherapeutic international normalized ratio values by using patient self-management, more frequent international normalized ratio monitoring, pharmacogenetic dosing, or anticoagulation clinics. Risk-prediction schemes also allow for more efficient clinical trials. Using the SPAF, Framingham, or CHADS<sup>2</sup> scheme, investigators could selectively recruit high-risk patients, resulting in a clinical trial with smaller sample size, greater power, or shorter duration of follow-up.

Limitations

Individuals who enroll in clinical trials may not represent the general population. In particular, SPORTIF did not have an adequate sample size for low-risk cohorts as identified by several schemes, thereby impairing the performance of all schemes to discriminate risk. Evaluating all of the prediction schemes in a population with a broader spectrum of risk could validate these findings.

Conclusions

In this large, prospective cohort of AF patients with risk factors for stroke who were randomized to warfarin or ximelagatran therapy, CHADS<sub>2</sub>, SPAF, and Framingham schemes had a predictive accuracy significantly greater than expected by chance. Future trials should quantify the benefit of newer strategies or novel anticoagulants in high-risk patients identified by these schemes.

Source of Funding

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Disclosures

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References


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