Selecting Patients With Atrial Fibrillation for Anticoagulation

Stroke Risk Stratification in Patients Taking Aspirin

Brian F. Gage, MD, MSc; Carl van Walraven, MD, FRCP, MSc; Lesly Pearce, MS; Robert G. Hart, MD; Peter J. Koudstaal, MD; B.S.P. Boode, MD; Palle Petersen, MD, PhD

Background—The rate of stroke in atrial fibrillation (AF) depends on the presence of comorbid conditions and the use of antithrombotic therapy. Although adjusted-dose warfarin is superior to aspirin for reducing stroke in AF, the absolute risk reduction of warfarin depends on the stroke rate with aspirin. This prospective cohort study tested the predictive accuracy of 5 stroke risk stratification schemes.

Methods and Results—The study pooled individual data from 2580 participants with nonvalvular AF who were prescribed aspirin in a multicenter trial (Atrial Fibrillation, Aspirin, Anticoagulation I study [AFASAK-1], AFASAK-2, European Atrial Fibrillation Trial, Primary Prevention of Arterial Thromboembolism in patients with nonrheumatic Atrial Fibrillation in primary care study, and Stroke Prevention and Atrial Fibrillation [SPAF]-III high risk or SPAF-III low risk). There were 207 ischemic strokes during 4887 patient-years of aspirin therapy. All schemes predicted stroke better than chance, but the number of patients categorized as low and high risk varied substantially. AF patients with prior cerebral ischemia were classified as high risk by all 5 schemes and had 10.8 strokes per 100 patient-years. The CHADS2 scheme (an acronym for Congestive heart failure, Hypertension, Age >75, Diabetes mellitus, and prior Stroke or transient ischemic attack) successfully identified primary prevention patients who were at high risk of stroke (5.3 strokes per 100 patient-years). In contrast, patients identified as high risk by other schemes had 3.0 to 4.2 strokes per 100 patient-years. Low-risk patients identified by all schemes had 0.5 to 1.4 strokes per 100 patient-years of therapy.

Conclusions—Patients with AF who have high and low rates of stroke when given aspirin can be reliably identified, allowing selection of antithrombotic prophylaxis to be individualized. (Circulation. 2004;110:2287-2292.)

Key Words: anticoagulants • aspirin • atrial fibrillation • risk factors • stroke

The rate of stroke in nonvalvular atrial fibrillation (AF) ranges widely and depends on the presence of prior cerebral ischemia, comorbid conditions, and use of antithrombotic therapy. Without antithrombotic therapy, the rate varies from fewer than 2 to more than 10 strokes per 100 patient-years.1–7 Although adjusted-dose warfarin is superior to aspirin for reducing stroke in AF patients, the absolute risk reduction is determined by the stroke risk with aspirin therapy.8,9 Thus, quantifying the risk of stroke is crucial for determining which AF patients would benefit most from warfarin therapy. Patients whose risk is less than ~2 strokes per 100 patient-years with aspirin have little to gain from warfarin therapy; for these patients, the risks of warfarin tend to outweigh any benefits.9–11 A risk stratification scheme that reliably identified these low-risk patients could spare them the risks, inconvenience, and costs associated with anticoagulation. In contrast, for AF patients whose risk exceeds 4 strokes per 100 patient-years of aspirin therapy, warfarin therapy consistently improves quality-adjusted survival.4,10,12 Between these 2 extremes are patients for whom the key issue is whether stroke risk can be quantified reliably so that antithrombotic therapy can be judiciously selected on the basis of stroke risk, hemorrhage risk, and individual preferences.10,13,14 Risk stratification schemes that accurately and reliably stratify stroke risk could influence the antithrombotic management of millions of people who have AF. Because patients with a prior stroke or transient ischemic attack (TIA) are at high risk of stroke, the greatest need is to quantify stroke risk in the AF primary prevention population. Here, we use prospective data to test the predictive accuracy of 5 widely available stroke risk stratification schemes and provide reliable guidance to clinicians selecting antithrombotic therapy.


Methods

Risk Stratification Schemes

Multivariate analyses of prospective cohorts of AF patients who were prescribed aspirin or no antithrombotic therapy yielded independent predictors of stroke that formed the basis of 5 previously published risk stratification schemes (Appendix). In 1994, the Atrial Fibrillation Investigators (AFI) conducted a multivariate analysis of pooled data from 1593 untreated AF patients in 5 randomized clinical trials. Participants with prior cerebral ischemia (either stroke or TIA), hypertension, or diabetes mellitus were at high risk of stroke; patients without these risk factors were at moderate risk of stroke if older than 65 years and at low risk otherwise (Table 1). The Stroke Prevention and Atrial Fibrillation (SPAF) investigators developed a classification scheme from 854 SPAF I and II participants treated with aspirin. Four factors independently predicted a high risk of stroke: prior cerebral ischemia, the combination of age greater than 75 years plus female gender, left ventricular dysfunction (defined as recent clinical heart failure or left ventricular fractional shortening $\leq 25\%$ by echocardiography), and systolic blood pressure $>160$ mm Hg (Table 1). SPAF participants with a history of hypertension but blood pressure $\leq 160$ mm Hg were found to have a moderate risk ($=3$ strokes per 100 patient-years), and participants with none of these factors were at low risk of stroke (Table 1).

In 1998 and 2001, the American College of Chest Physicians (ACCP) Consensus Conference on Antithrombotic Therapy classified participants into the appropriate strata of each scheme and excluded others. We excluded schemes that were based entirely on retrospective data. We excluded 2 schemes that were based on data used in the present analysis and another that were based on data from a single trial. We excluded schemes that were not clear.

In 2001, an amalgamation of the AFI and SPAF schemes led to the CHADS$_2$ scheme. The CHADS$_2$ acronym was derived from the CHF (class I in AF patients who took aspirin at dosages ranging between 75 and 325 mg daily in 6 prospective trials made up the validation cohort (Table 2). To validate the risk stratification schemes in an independent cohort of AF patients, patient data that were used to derive any of the 4 classification schemes were excluded from this analysis.

We used patient data from 6 prospective randomized trials. In 4 trials, participants were prescribed aspirin alone: the Atrial Fibrillation, Aspirin, Clopidogrel, and Enoxaparin in Nonvalvular Atrial Fibrillation study (ACAF; n = 336) study, the Primary prevention of Atrial Fibrillation, Stroke, and Vascular Events in Patients with Nonvalvular Atrial Fibrillation in Primary Care study (PAPA; n = 319), the European Atrial Fibrillation Trial (EAFIT; n = 404), and the low-risk SPAF III study (n = 891; 1 additional SPAF patient was excluded for missing information). From the fifth trial, AFASAK-2, we included participants who were prescribed aspirin, either alone (n = 169) or in combination with an ineffective, 1.25-mg dose of warfarin (n = 171). From the sixth trial, high-risk SPAF III, we included participants (n = 290) who were prescribed aspirin in combination with low-dose warfarin (median dose 2 mg/d) if their international normalized ratio never exceeded 1.4 during follow-up. Adherence to aspirin therapy exceeded 85% in the studies in which it was reported.

Research coordinators and physicians recorded baseline patient characteristics at the time of enrollment in the original trials. We classified participants into the appropriate strata of each scheme.

### Table 1. Stroke Risk Stratification Schemes

<table>
<thead>
<tr>
<th>Scheme</th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFI</td>
<td>0.3–3.1</td>
<td>3.5–4.3</td>
<td>4.9–8.1</td>
</tr>
<tr>
<td>SPAF</td>
<td>0.5–2.3</td>
<td>1.7–4.7</td>
<td>4.5–7.8</td>
</tr>
</tbody>
</table>
| ACCP   | ... | ... | ...
| CHADS$_2$ | 1.2–3.0 | 2.8–4.0 | 5.9–18.2 |
| Framingham | 1.0–1.9 | 2.3–4.0 | 4.2–27.7 |

### Table 2. Study Participants

<table>
<thead>
<tr>
<th>Description of the Validation Population</th>
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<tbody>
<tr>
<td>Prescribed aspirin: 2580 (100)</td>
</tr>
<tr>
<td>Women: 943 (37)</td>
</tr>
<tr>
<td>Mean age, y (SD): 72 (9)</td>
</tr>
<tr>
<td>Age $&gt;75$ y: 1003 (39)</td>
</tr>
<tr>
<td>Hypertension: 1188 (46)</td>
</tr>
<tr>
<td>SBP $\geq 160$ mm Hg: 645 (25)</td>
</tr>
<tr>
<td>Heart failure: 655 (25)</td>
</tr>
<tr>
<td>Diabetes mellitus: 346 (13)</td>
</tr>
<tr>
<td>Prior stroke or TIA: 566 (22)</td>
</tr>
<tr>
<td>Prior MI or angina: 464 (18)</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; MI, myocardial infarction. Values are n (%), except for age.
TABLE 3. Validation of Stratification Schemes for Primary Prevention of Stroke in 2014 Participants Prescribed Aspirin

<table>
<thead>
<tr>
<th>Scheme</th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFI</td>
<td>0.9 (0.3–2.3; n=235)</td>
<td>1.7 (1.1–2.5; n=781)</td>
<td>3.5 (2.7–4.5; n=998)</td>
</tr>
<tr>
<td>SPAF</td>
<td>1.1 (0.7–1.8; n=668)</td>
<td>2.7 (1.8–4.0; n=462)</td>
<td>3.6 (2.7–4.7; n=884)</td>
</tr>
<tr>
<td>ACCP</td>
<td>0.5 (0.1–2.2; n=175)</td>
<td>1.0 (0.4–2.2; n=296)</td>
<td>3.0 (2.5–3.8; n=1543)</td>
</tr>
<tr>
<td>CHADS2</td>
<td>0.8 (0.4–1.7; n=469)</td>
<td>2.7 (2.2–3.4; n=1322)</td>
<td>5.3 (3.3–8.4; n=223)</td>
</tr>
<tr>
<td>Framingham</td>
<td>1.4 (1.0–2.1; n=983)</td>
<td>3.2 (2.4–4.3; n=700)</td>
<td>4.2 (2.8–6.1; n=331)</td>
</tr>
</tbody>
</table>

Table excludes participants (n=566) who previously had a stroke or TIA. Stroke rates (with 95% CIs) are from strata identified by clinical factors alone; echocardiographic results were not available.

Results

Characteristics of the Validation Cohort

The 2580 participants had a mean age of 72 years, 38% were female, and 22% had suffered a prior stroke or TIA (Table 2). The most frequent risk factor was hypertension, which was present in 46%, and the least common was diabetes, with a 13% prevalence. Participants were followed up for a mean of 1.9 years (maximum 6.6 years). During 4887 patient-years of follow-up, there were 207 ischemic strokes, for an overall incidence rate of 4.2 strokes per 100 patient-years during aspirin therapy. The rate among the 2014 primary prevention participants without prior cerebral ischemia was 2.5 strokes per 100 patient-years of aspirin; for the 566 participants with a prior stroke or TIA, the rate was 10.8 per 100 patient-years of aspirin.

Stroke Rates According to Predicted Risk for Each Scheme

All schemes stratified the risk of ischemic stroke significantly better than chance (log-rank P<0.001 for all schemes), but the number of AF patients categorized as at high, moderate, and low risk varied substantially (Table 3). The agreement between schemes was variable, with weighted κ-values ranging from a low of 0.13 (ACCP versus Framingham) to a high of 0.58 (ACCP versus AFI).

Comparison of the Classification Schemes

The stroke rates (95% CI) per 100 patient-years of aspirin rose with increasing CHADS2 scores: 0.8 (0.4 to 1.7; n=469) with 0 points; 2.2 (1.6 to 3.1; n=752) with 1 point; 4.5 (3.5 to 5.9; n=670) with 2 points; 8.6 (6.8 to 11.0; n=428) with 3 points; 10.9 (7.8 to 15.2; n=200) with 4 points; 12.3 (6.6 to 22.9; n=56) with 5 points; and 13.7 (2 to 97; n=5) with 6 points. Rates (95% CI) per 100 patient-years of aspirin in other high-risk patients were lower than in the highest CHADS2 cohorts: 6.1 (5.3 to 7.1) by AFI criterion, 6.5 (5.6 to 7.6) by SPAF, 5.1 (4.4 to 5.8) by ACCP, and 7.9 (6.5 to 9.7) for Framingham score >13.

Among primary prevention participants, CHADS2 identified participants at high risk for stroke: primary prevention participants with 3 or 4 points averaged 5.3 (95% CI 3.3 to 8.4) strokes per 100 patient-years. In contrast, participants identified by other schemes as high risk had rates of 3.0 to 4.2 strokes per 100 patient-years (Table 3). The use of a higher Framingham threshold (>15 rather than >13 points; Table 3) identified 144 participants whose stroke rate was only 3.9.

A Cox proportional hazards model quantified the ability to discriminate between low- and high-risk patients by the likelihood ratio χ² test. The χ² (SD) was 67 (16) for AFI, 73 (16) for SPAF, 44 (11) for ACCP, 98 (19) for CHADS2, and 89 (20) for Framingham (P<0.001 for CHADS2 versus the other schemes).
Collapsing CHADS$_2$ into 3 strata (0, 1 to 2, and 3 to 6) yielded a $\chi^2$ value of 86, and collapsing Framingham into 3 strata (0 to 7, 8 to 13, and >13) yielded a value of 69. When only primary prevention patients were analyzed, $\chi^2$ values were lower, but the pattern was similar: AFI 18, SPAF 17, ACCP 17, CHADS$_2$ 22 (20 with 3 strata), and Framingham 16 ($P<0.001$ for CHADS$_2$ versus other schemes).

The $c$-statistics (SD) were 0.63 (0.01) for AFI, 0.64 (0.01) for SPAF, 0.58 (0.01) for ACCP, 0.70 (0.02) for CHADS$_2$, and 0.69 (0.02) for Framingham ($P<0.001$ for CHADS$_2$ versus other schemes). When participants with a prior stroke or TIA were excluded, $c$-statistics (SD) were 0.61 (0.02) for AFI, 0.61 (0.02) for SPAF, 0.58 (0.02) for ACCP, 0.63 (0.03) for CHADS$_2$, and 0.62 (0.03) for Framingham.

Identification of Patients Whose Stroke Rate Was Low With Aspirin Therapy

ACCP criteria classified the fewest participants as low risk (n=182). In contrast, SPAF classified 668 participants as low risk (Table 3). Primary prevention participants with a Framingham score of 4 or less (n=502) or 7 or less (n=983) both averaged 1.4 strokes per 100 patient-years. Primary prevention participants with 7 or fewer Framingham points who were not considered low risk by SPAF averaged 2.2 strokes per 100 patient-years; primary prevention participants with 7 or fewer Framingham points who had 1 or more CHADS$_2$ points averaged 1.9 strokes per 100 patient-years.

Discussion

This study of 2580 participants to whom aspirin had been prescribed confirms that AF populations with high and low stroke risks can be identified prospectively. Patients with a prior stroke or TIA averaged 10.8 strokes per 100 patient-years despite aspirin therapy. For these patients, it is clear that the benefits of anticoagulant therapy outweigh the risks.30,32,38

Primary prevention patients whose stroke risk exceeds $\approx$4 per 100 patient-years of aspirin also benefit from warfarin therapy.4,10,12 These patients were reliably identified by a CHADS$_2$ score $\geq$3. Such patients averaged 5.3 strokes per 100 patient-years of aspirin. The number needed to treat with warfarin instead of aspirin for 1 year to prevent 1 stroke would be $\approx$30 for these patients.9,12 High-risk primary prevention patients identified by the other schemes had stroke rates of only 3.0 to 4.2.

In contrast, all schemes successfully identified low-risk patients whose stroke rate was 1.4 or lower per 100 patient-years of aspirin, but the agreement between schemes was poor. Experts and patients typically prefer aspirin to warfarin when the risk is less than $\approx$2 strokes per 100 patient-years of aspirin.9-11 For these AF patients, the number needed to treat with warfarin for 1 year to prevent 1 stroke exceeds 100. The ability to characterize low-risk AF patients with confidence allows clinicians to identify patients who can safely be treated with aspirin, sparing them the risk of bleeding, cost, and inconvenience from anticoagulant therapy.39,40 Although the Framingham scheme identified the largest fraction of low-risk patients (almost half of the primary prevention cohort had a Framingham score of 7 or less), the additional low-risk patients identified had $\approx$2 strokes per 100 patient-years, a rate substantially greater than other low-risk cohorts.

For patients whose stroke risk is 2 to 4 per 100 patient-years of aspirin therapy, many experts offer warfarin,41,42 whereas others offer aspirin,43,44 depending on risk of hemorrhage and patient preferences. In clinical trials, warfarin increased the risk of major hemorrhage 1.7-fold compared with aspirin.9 Outside of trials, the risk of hemorrhage was greater,45,46 depending on how warfarin was monitored49 and risk factors for hemorrhage.48 How patients trade off the risk of stroke, risk of hemorrhage, and the aggravation of taking and monitoring anticoagulant therapy depends on individual preferences.10,13,14

The use of data from clinical trial cohorts confers both strengths and limitations to the present study. One strength is that similar sets of comorbid conditions were collected at baseline across different trials. A second strength is that ischemic strokes were identified prospectively by clinical examination and confirmed by computerized tomography. A third is that all patients received aspirin, which allowed us to quantify the stroke rate with this ubiquitous, inexpensive therapy. A fourth strength is that none of the patients included in these analyses were included as part of the derivation cohorts for any of the schemes. Finally, because the schemes were derived primarily from patients assigned to no antithrombotic therapy, the present study demonstrates that the schemes (especially CHADS$_2$) are valid predictors of stroke in patients prescribed aspirin.

One limitation is that patients with contraindications to warfarin therapy were included in only 1 of the 6 trials. The inclusion of more of these patients would have provided greater generalizability, but such patients were excluded from clinical trials. Second, echocardiographic results were not available, which would have allowed us to assess whether they would have improved the predictive accuracy of the schemes that consider left ventricular systolic dysfunction as a stroke risk factor. Thus, the SPAF criteria for impaired left ventricular function could not be tested, and a history of heart failure was used instead. A finding of significant systolic dysfunction by echocardiography primarily would be relevant to patients at low risk of stroke on the basis of clinical factors.24,49

Recent retrospective studies of other AF populations further validate CHADS$_2$. For example, enrollees of Kaiser Permanente (Northern California) who were not prescribed warfarin (4% of whom had a prior stroke) had a very low stroke rate (0.5 per 100 patient-years) if their CHADS$_2$ score was 0. Their stroke rates were greater with greater CHADS$_2$ scores: 1.5 for 1 point, 2.5 for 2 points, 5.3 for 3 points, 6.0 for 4 points, and 6.9 for 5 or 6 points.46 Although other schemes were not evaluated by these studies, it confirms the ability of CHADS$_2$ to identify low- and high-risk patients reliably.

In the future, a more accurate prediction rule for stroke may be possible by incorporating additional factors. For example, left ventricular systolic dysfunction detected by 2D transthoracic echocardiography is an independent risk factor for stroke in AF.24 Also, it seems likely that hormone replacement therapy21,50 and cigarette smoking51 increase the risk of stroke in AF, whereas modest alcohol consumption may decrease it.21 Finally, future studies will determine whether biochemical markers of inflammation (eg, C-reactive protein) or endothelial dysfunction (eg, von Willebrand factor) will help clinicians predict stroke in the AF population.
Appendix

### TABLE 4. Definitions Used by Stroke Risk Stratification Schemes

<table>
<thead>
<tr>
<th>Scheme</th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFI (1994)</td>
<td>Not moderate or high risk</td>
<td>Age ≥65 years but not high risk</td>
<td>Prior ischemia, HTN, DM</td>
</tr>
<tr>
<td>SPAF (1995, 1998)</td>
<td>Not moderate or high risk</td>
<td>HTN but not high risk</td>
<td>Prior ischemia, women aged &gt;75 years, recent CHF or LV fractional shortening ≤25%, SBP &gt;160 mm Hg</td>
</tr>
<tr>
<td>ACCP (1998, 2001)</td>
<td>Not moderate or high risk</td>
<td>1 of the following: age 65–75 years, DM, or CAD but not high risk</td>
<td>Prior ischemia, HTN, CHF, age &gt;75 years, or 2 or more moderate risk factors</td>
</tr>
<tr>
<td>CHADS, (2001)</td>
<td>Score = +1 for CHF, +1 for HTN, +1 for age &gt;75 years, +1 for DM, +2 points for a prior stroke or TIA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Framingham (2003)</td>
<td>Score = +6 for prior ischemia, + 0 to 4 for blood pressure, +4 for diabetes mellitus, + 0 to 10 for age, +6 for female gender</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HTN indicates hypertension; DM, diabetes mellitus; CHF, congestive heart failure; LV, left ventricular; SBP, systolic blood pressure; and CAD, coronary artery disease.

Acknowledgments

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Disclosure

Several of the authors were involved in the development of the risk stratification schemes tested in these analyses: AFI (Drs Hart and Petersen), SPAF (Drs Hart and L. Pearce), and CHADS, (Dr Gage).

References


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