Identifying independent risk factors for stroke in patients with atrial fibrillation is important for 2 main reasons: it sheds light on stroke pathogenesis associated with this common cardiac dysrhythmia, and it allows stratification of stroke risk for individual patients. Both are keys to prevention of the unduly large cardioembolic brain infarcts that complicate atrial fibrillation. Among nonvalvular atrial fibrillation patients, the absolute risk of stroke averages 3% to 4% per year, but it varies 20-fold depending on patient age and other clinical features.\(^1,^2\) Hence, stroke risk stratification allows the absolute benefits of prophylactic antithrombotic therapy to be estimated for individual patients.

Since the initial analysis of the pooled control groups of 5 randomized clinical trials in 1994,\(^3\) several studies analyzing stroke risk factors in nonvalvular atrial fibrillation patients using multivariate analysis have yielded 4 consistent predictors: increasing age, hypertension/systolic blood pressure, diabetes, and prior embolism (Table 1).\(^1\) Prior stroke/TIA is the most powerful risk factor and is associated with high rates of stroke (>5% per year, averaging 10% per year) warranting anticoagulation, even in atrial fibrillation patients without other risk factors.\(^1\) Female sex has been less consistently linked to stroke risk, although independently predictive in 3 studies.\(^1\) Unexpectedly, heart failure has not been an independent predictor of stroke in atrial fibrillation patients. Further, a recurrent paroxysmal pattern (as opposed to persistent or permanent atrial fibrillation) in elderly patients was not independently predictive of reduced stroke risk in any of 4 studies in which it was assessed.

What are the pathogenetic implications? The 4 most consistent risk factors for stroke in atrial fibrillation patients (ie, prior stroke/TIA, advancing age, hypertension, and diabetes) are also risk factors for stroke among persons without atrial fibrillation. However, the absolute stroke rates associated with these risk factors are several times higher among atrial fibrillation patients compared with risk factor–specific age-adjusted rates in patients without atrial fibrillation. Hypertension is associated with stasis of flow and thrombus in the left atrial appendage and with cardioembolic strokes in atrial fibrillation patients (Figure).\(^9\)–\(^11\) Left atrial appendage flow velocities, strongly and inversely associated with appendage thrombi, decrease with advancing age.\(^11\) Diabetes may be a marker of a prothrombotic state favoring left atrial thrombus formation.\(^12\) The large relative risk reduction of ischemic strokes by anticoagulation over aspirin in atrial fibrillation

### Table 1. Independent Risk Factors for Stroke in Atrial Fibrillation Patients: Summary of Studies Using Multivariate Analysis\(^*\)

<table>
<thead>
<tr>
<th>Feature</th>
<th>No. of Positive Studies/Total</th>
<th>Pooled Relative Risk Estimate(^\ast) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior stroke or TIA</td>
<td>5 of 5</td>
<td>2.5 (1.9–3.3)</td>
</tr>
<tr>
<td>Increasing age per decade</td>
<td>6 of 6</td>
<td>1.4 (1.3–1.6)</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>4 of 5</td>
<td>1.9 (1.5–2.4)</td>
</tr>
<tr>
<td>Systolic blood pressure (\geq160)†</td>
<td>3 of 3</td>
<td>1.4 (1.2–1.6)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4 of 6</td>
<td>1.7 (1.5–2.1)</td>
</tr>
<tr>
<td>Female sex</td>
<td>3 of 6</td>
<td>NC</td>
</tr>
<tr>
<td>Left ventricular dysfunction by echocardiography</td>
<td>1 of 3</td>
<td>NC</td>
</tr>
<tr>
<td>Heart failure</td>
<td>0 of 4‡</td>
<td>NC</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>0 of 5</td>
<td>NC</td>
</tr>
<tr>
<td>Paroxysmal vs permanent pattern</td>
<td>0 of 4</td>
<td>NC</td>
</tr>
</tbody>
</table>

\(^\ast\)Adapted from the Stroke Risk in Atrial Fibrillation Working Group\(^1\) with addition of data from Healey et al\(^4\); studies of anticoagulated patients were excluded. Pooled relative risks derived from maximum likelihood methods. Other independent risk factors that were statistically significant in at least 1 multivariate analysis include hormone replacement therapy\(^6\) and left atrial thrombus detected by transesophageal echocardiography.\(^1\) A recent multivariate analysis of 8932 patients receiving placebo, aspirin, or warfarin in 12 randomized trials was confirmatory.\(^6\)

†Relative risk estimate for a 30-mm Hg difference in 2 trials combined\(^5,^8\); estimate for systolic blood pressure is \(\geq160\) mm Hg.

‡Significant \((RR=1.7, p=0.03) in 1 subgroup analysis of patients undergoing echocardiography.\(^7\)
patients with these risk factors except diabetes sharply differs from the lack of superiority of warfarin over aspirin in patients with noncardioembolic cerebrovascular diseases, indirectly supporting a cardioembolic etiology in atrial fibrillation patients. A smaller reduction by warfarin over aspirin has been reported in diabetics, suggesting that diabetes may be associated with noncardioembolic strokes from which elderly atrial fibrillation patients are not spared.

Heart failure alters left atrial dynamics and should logically be a predictor of left atrial thrombus formation and, consequently, of embolic stroke. Even recent heart failure (ie, within 3 months of study entry) failed to emerge from multivariate models as independently predictive of stroke. Heart failure can be difficult to accurately diagnose in elderly people with multiple comorbidities, potentially blunting its predictive power, yet it was diagnosed by cardiology specialists in several studies. Heart failure was significantly predictive of stroke in a pooled analysis of 3 trials, but its independent predictive value was not significant when left ventricular function by echocardiography was added to the prediction model. Left ventricular systolic dysfunction by echocardiography might have the advantage of being a current assessment of ventricular function over a clinical diagnosis of a history of heart failure. Ventricular diastolic dysfunction is less readily assessed by echocardiography and may have more influence on left atrial dynamics.

Stroke Risk Stratification Schemes

More than a dozen published stroke risk stratification schemes have resulted in widely varying treatment recommendations, confusion among clinicians, and nonuniform treatment. Currently there is an emerging consensus based on 3 prominent schemes (Table 2) that apply to both patients with paroxysmal and permanent atrial fibrillation. The popular CHADS2 scheme uses a point system with 1 point given for each of Congestive heart failure, Hypertension, Age, Diabetes, Stroke/TIA, and Heart failure.

Table 2. Stroke Risk Stratification in Atrial Fibrillation: Three Prominent Schemes

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure*–1 point</td>
<td>High risk</td>
<td>High risk</td>
</tr>
<tr>
<td>Hypertension†–1 point</td>
<td>Prior thromboembolism‡</td>
<td>Prior thromboembolism‡</td>
</tr>
<tr>
<td>Age &gt;75 yrs–1 point</td>
<td>≥2 moderate risk features</td>
<td>≥2 moderate risk features</td>
</tr>
<tr>
<td>Diabetes–1 point</td>
<td>Moderate risk</td>
<td>Intermediate risk</td>
</tr>
<tr>
<td>Stroke/TIA ≤ 2 points</td>
<td>Age &gt;75 years</td>
<td>Age &gt;75 years</td>
</tr>
<tr>
<td>Heart failure**</td>
<td>Hypertension†</td>
<td>History of hypertension†</td>
</tr>
<tr>
<td>Low risk=0 points</td>
<td>Diabetes</td>
<td>Diabetes</td>
</tr>
<tr>
<td>Moderate risk=1 point</td>
<td>Left ventricular ejection fraction ≤35% or fractional shortening &lt;25%</td>
<td>Moderately to severely impaired left ventricular systolic function¶</td>
</tr>
<tr>
<td>High risk ≥2 points</td>
<td>Low risk§</td>
<td>Low risk§</td>
</tr>
</tbody>
</table>

ACC/AHA/ESC indicates American College of Cardiology/American Heart Association/European Society of Cardiology; ACCP, American College of Chest Physicians.

*Recent heart failure exacerbation was used in the original stratification, but subsequently any prior or current heart failure has supplanted.
†A history of hypertension, not specifically defined.
‡Prior stroke, TIA, or systemic embolism.
§“Less well-validated” risk factors were female sex, coronary artery disease, and age 65 to 74 years. Unclear whether patients with ≥1 should be categorized as moderate risk: antithrombotic therapy with either vitamin K antagonists or aspirin is reasonable depending on bleeding risks, ability to safely sustain anticoagulation, and patient preferences.
¶Echocardiographic parameters not specifically defined.
§In previous studies, moderate risk was typically defined as CHADS2 scores of 1 or 2. The current definition makes the 3 schemes very similar.
**Not clear whether history of heart failure, recent heart failure, or current heart failure.
Hypertension, Age ≥75, and Diabetes mellitus and 2 points for prior Stroke/TIA.18 If CHADS2 score of 1 is defined as moderate or intermediate risk, the 3 schemes are very similar, the remaining 2 guidelines using CHADS2 variables with the addition of echocardiographic assessment of left ventricular systolic dysfunction.19,20 The addition of left ventricular systolic dysfunction by echocardiography to the CHADS2 scheme shifts classification of about 5% of atrial fibrillation patients to a higher strata. A representative cohort of atrial fibrillation patients would be categorized as 20% low risk, 34% intermediate risk, and 46% high risk.2 The clinical value of these schemes is dependent on the threshold stroke rates that would alter antithrombotic prophylaxis: their ability to accurately discriminate patients with an approximately 2%/yr stroke risk (ie, considered to be moderate or intermediate risk by many) from those with higher or lower risks. Aggregate data from 7 studies support that a CHADS2 score of 1 carries an ischemic stroke risk of about 2%/yr, with no data for the other 2 (very similar) schemes (Table 3).

Despite the emerging consensus, many important issues are unresolved. These schemes did not perform optimally when tested in a large administrative outpatient database in which overall stroke rates were low,27 and there is a paucity of data about the absolute stroke rates associated with classification as high risk. It is also unclear whether and how heart failure, not an independent predictor of stroke in atrial fibrillation patients as discussed above, contributes to risk stratification. Current schemes do not take into account the duration, severity, or treatment of the key predictors. Does well-treated hypertension carry the same risk as untreated hypertension in atrial fibrillation patients? Probably not.28,29 Markers of a prothrombotic state contributing to left atrial appendage thrombus formation have been explored in many studies, but their contribution to risk stratification is ill-defined.30,31 Much work remains to improve stroke risk stratification for the millions with nonvalvular atrial fibrillation.

Disclosures

None.

References


Table 3. Ischemic Stroke Rates Associated With Classification as Moderate-Risk*

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>n</th>
<th>f/u</th>
<th>Antiplatelet Therapy</th>
<th>Time Period</th>
<th>Stroke Rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gage et al17</td>
<td>HDC</td>
<td>463</td>
<td>1.2</td>
<td>31% ASA</td>
<td>late 1990s</td>
<td>2.8%/yr (2.0–3.8)</td>
</tr>
<tr>
<td>Gage et al23</td>
<td>RCTs</td>
<td>752</td>
<td>1.9</td>
<td>100% ASA</td>
<td>1987–1996</td>
<td>2.2%/yr (1.6–3.1)</td>
</tr>
<tr>
<td>Go et al14</td>
<td>OLC</td>
<td>∼1628</td>
<td>2.2</td>
<td>∼45% ASA</td>
<td>1996–1999</td>
<td>1.5%/yr (1.2–1.9)</td>
</tr>
<tr>
<td>Healey et al4</td>
<td>RCT</td>
<td>2436</td>
<td>1.3</td>
<td>100% CPG + ASA</td>
<td>2003–2006</td>
<td>1.3%/yr (0.9–1.7)†</td>
</tr>
<tr>
<td>Ruiz Ortiz et al24</td>
<td>OLC</td>
<td>81</td>
<td>1.8</td>
<td>NR</td>
<td>2000–2006</td>
<td>2.8%/yr (1.1–5.7)</td>
</tr>
<tr>
<td>Mant et al26§</td>
<td>RCT</td>
<td>221</td>
<td>2.3</td>
<td>100% ASA</td>
<td>2003–2006</td>
<td>1.4%/yr (0.6–2.9)</td>
</tr>
<tr>
<td>ACTIVE A25</td>
<td>RCT</td>
<td>1338</td>
<td>3.6</td>
<td>100% ASA</td>
<td>2003–2008</td>
<td>2.4%/yr (2.0–2.9)</td>
</tr>
<tr>
<td>ACTIVE A25</td>
<td>RCT</td>
<td>1360</td>
<td>3.6</td>
<td>100% ASA + CPG</td>
<td>2003–2008</td>
<td>1.6%/yr (1.3–2.0)</td>
</tr>
</tbody>
</table>

AHA/ACC/ESC criteria for moderate-risk

None identified

ACCP Practice Guidelines criteria for intermediate-risk

None identified

n indicates number of moderate-risk patients; f/u, average follow-up in patient-years; yr, year; CI, confidence interval; RCT, randomized clinical trial; HDC, hospital discharge cohort; OLC, outpatient longitudinal cohort; NR, not reported; ASA, acetylsalicylic acid; CPG, clopidogrel; ACC/AHA/ESC, American College of Cardiology/American Heart Association/European Society of Cardiology; ACCP, American College of Chest Physicians.

*See Table 2 for criteria for moderate-risk for the 3 risk stratification schemes. The stroke rate for several studies included 5% to 10% non-CNS emboli14,26 or intracerebral hemorrhages,4,25 so the ischemic stroke rate is estimated as 5% to 10% lower. For low-risk patients with a CHADS2 (score = 0), reported annual stroke rates in studies excluding TIA were 0%,14 0.5%,13 0.8%,23 and 1.7%.8
†There is an apparent discrepancy in the publication between the rate given in the text (1.25%/yr) vs Table 2 (1.21%/yr).4
‡About 25% of “stroke” events were transient ischemic attacks.
§Personal communication, J. Mant on behalf of the Birmingham Atrial Fibrillation Trial in the Aged investigators.26 All were over age 75 years as the reason for CHADS2 score = 1.


Key Words: atrial fibrillation ■ stroke ■ risk factors ■ clinical prediction rules ■ risk stratification
Current Status of Stroke Risk Stratification in Patients With Atrial Fibrillation
Robert G. Hart and Lesly A. Pearce

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