Factors Associated With Ischemic Stroke During Aspirin Therapy in Atrial Fibrillation
Analysis of 2012 Participants in the SPAF I–III Clinical Trials

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Background and Purpose—Nonvalvular atrial fibrillation (AF) is a strong, independent risk factor for stroke, but the absolute rate of stroke varies widely among AF patients, importantly influencing the potential benefit of antithrombotic prophylaxis. We explore factors associated with ischemic stroke in AF patients taking aspirin.

Methods—We performed multivariate logistic regression analysis of 2012 participants given aspirin alone or in combination with low, inefficacious doses of warfarin in the Stroke Prevention in Atrial Fibrillation I–III trials followed for a mean of 2.0 years, during which 130 ischemic strokes were observed.

Results—Age (relative risk [RR] = 1.8 per decade, \( P < 0.001 \)), female sex (RR = 1.6, \( P = 0.01 \)), history of hypertension (RR = 2.0, \( P < 0.001 \)), systolic blood pressure >160 mm Hg (RR = 2.3, \( P < 0.001 \)), and prior stroke or transient ischemic attack (RR = 2.9, \( P < 0.001 \)) were independently associated with increased stroke risk. Regular consumption of \( \geq 14 \) alcohol-containing drinks per week was associated with reduced stroke risk (adjusted RR = 0.4, \( P = 0.04 \)). Among SPAF III participants, estrogen hormone replacement therapy was associated with a higher risk of ischemic stroke (adjusted RR = 3.2, \( P = 0.007 \)). With the use of these variables, a risk stratification scheme for primary prevention separated participants into those with high (7.1%/y, 22% of the cohort), moderate (2.6%/y, 37% of the cohort), and low (0.9%/y, 41% of the cohort) rates of stroke. Ischemic strokes in low-risk participants were less often disabling (\( P < 0.001 \)).

Conclusions—Patients with AF who have high and low rates of stroke during treatment with aspirin can be identified. However, validation of our risk stratification scheme is necessary before it can be applied with confidence to clinical management. Postmenopausal estrogen replacement therapy and moderate alcohol consumption may additionally modify the risk of stroke in AF, but these findings require confirmation. (Stroke. 1999;30:1223-1229.)

Key Words: atrial fibrillation ■ cerebral embolism ■ estrogens ■ risk factors ■ stroke prevention

Atrial fibrillation (AF) is associated with a substantially increased risk of stroke, and treatment with adjusted-dose warfarin is highly efficacious for stroke prevention. The absolute rate of stroke varies widely according to age and the presence of coexistent vascular disease. AF patients with the highest absolute rates of stroke have the greatest magnitude of stroke reduction by warfarin, while AF patients with low stroke rates may not benefit substantially from lifelong anticoagulation. Hence, accurate estimate of the inherent stroke risk is an important component of the antithrombotic management of AF patients.

Factors associated with stroke among participants in the Stroke Prevention in Atrial Fibrillation (SPAF) I and II trials who received placebo or aspirin have been reported previously. Here, we pool participants from these trials with those from the recently completed SPAF III trial to explore factors associated with ischemic stroke in a large cohort of AF patients given aspirin alone or combined with low, inefficacious doses of warfarin. A risk stratification scheme is derived from factors independently associated with stroke and focuses on primary prevention, since the high rate of stroke associated with previous stroke or transient ischemic attack (TIA) is well documented.

Subjects and Methods

The design, participant features, and main results of the SPAF I, II, and III trials have been reported. In brief, participants were adults with documented sustained or recurrent AF without mitral stenosis or prosthetic cardiac valves who were recruited from inpatient and outpatient facilities at 25 clinical sites. These analyses included participants assigned to aspirin 325 mg/d (enteric-coated). In addition, 290 participants in the SPAF III randomized trial who were assigned to aspirin plus fixed, low-dose warfarin (mean daily dose = 2.1 mg) and whose international normalized ratios (INRs) during follow-up were \( \leq 1.4 \) were also included.
Stroke Atrial Fibrillation

Included. 2 This latter group was included because INRs <1.5 have been shown to have no substantial effect on stroke prevention in AF. 2,3,14 and these high-risk participants were observed to have a stroke rate of 12.3%/y, similar to that expected during treatment with aspirin alone. 6 Those with “lone” AF (ie, no associated cardiovascular disease) aged <60 years were excluded. Participants from SPAF I (n=521, 1985–1989), SPAF II (n=309, 1989–1992), and SPAF III (n=1182, 1993–1997) constituted the study population.

At study entry, all participants were assessed by physician investigators, coexistent illnesses were recorded with the use of specific definitions, and precordial echocardiography was performed. 8 Echocardiograms were interpreted locally by cardiologists using standard criteria, as reported previously. 3 Participants were followed every 3 to 6 months in the clinic to assess compliance and to detect strokes. Stroke events were verified and categorized as probably cardioembolic, probably noncardioembolic, or of uncertain cause by a central events committee who were unaware of treatment, using a clinical classification scheme. 9,10 Neuroimaging or autopsy was used to categorize strokes as ischemic versus hemorrhagic in 94%. Disabling strokes were conservatively defined as those with Rankin scores of II (impaired lifestyle) or more, assessed to 3 months later, while fatal stroke resulted in death within 30 days. For this analysis, participant follow-up was censored at the time of first ischemic stroke (ie, only 1 stroke per participant during follow-up was counted).

The following variables were initially considered in exploratory analyses, selected by the investigators on the basis of hypothetical links to stroke risk: age, sex, race, current tobacco smoker, ethanol consumption, prior stroke or TIA, history of hypertension, systolic (continuous and >160 mm Hg) and diastolic blood pressures at entry. diabetes mellitus, history of heart failure, recent (within 100 days) heart failure, intermittent AF, onset of AF within 1 year, prior myocardial infarction, any ischemic heart disease, ventricular rate, peripheral vascular disease, prior carotid endarterectomy or cervical bruit, pulse pressure, use of specific classes of medications (diuretics, β-blockers, insulin), and random serum cholesterol. Echocardiographic variables were left atrial diameter, left ventricular end-systolic and –diastolic dimensions, fractional shortening (continuous and ≤25%), mitral annular calcification (any and moderate to severe involving >30% of the annulus), severe mitral regurgitation, 16 qualitative abnormalities of left ventricular wall motion on 2-dimensional echocardiographic images, and left ventricular mass and mass index. Estrogen hormone replacement therapy and severity of hypertension were recorded only for SPAF III participants at entry.

Hypertension was diagnosed if blood pressures were either >160 mm Hg systolic or >90 mm Hg diastolic on repeated observations over ≥3 months or by use of long-term antihypertensive therapy if pretreatment blood pressure measurements were not available. 3 In SPAF III participants, hypertension was categorized as moderate to severe if diastolic blood pressure were consistently >100 mm Hg or multiple antihypertensive medications were prescribed. Systolic blood pressure >160 mm Hg was defined by taking 2 blood pressure measurements on separate days, with 1 systolic blood pressure >160 mm Hg and either the other >150 mm Hg or a documented systolic blood pressure measurement >160 mm Hg in the prior 3 months. 9

Distributions of baseline characteristics were compared between groups with the use of Student’s t test for continuous variables and a χ² test for categorical variables (Fisher’s exact test if any expected cell count was <5). The univariate association of ischemic stroke with a variable was estimated with a Cox proportional hazards model, with statistical significance determined by the likelihood ratio statistic. Factors independently associated with stroke were identified with forward stepwise Cox proportional hazards modeling techniques (likelihood ratio test) and combined by inspection to yield a risk stratification scheme. Stroke rates were calculated with person-years as the denominator, with 95% CIs computed by the Poisson distribution. Stroke rates were compared between groups with the use of a Poisson regression model (likelihood ratio statistic).

All tests were 2-sided, and statistical significance was accepted at the 0.05 level, with no adjustment made for multiple comparisons. Analyses were performed with SPSS/PC for Windows and EGRET statistical software.

Results

In the SPAF I–III trials, 1722 participants were assigned aspirin, and an additional 290 were given aspirin plus fixed, low-dose warfarin without substantial prolongation of their INR (mean INR=1.1 during follow-up). Of these 2012 participants, the mean age was 69±10 years, 28% were women, 27% had intermittent AF, and 52%, 9%, 15%, and 8% had histories of hypertension, myocardial infarction, diabetes, and prior stroke or TIA, respectively (Table 1). A history of clinical congestive heart failure was present in 19%, and fractional shortening by echocardiography was <25% in 12% of participants. Mean follow-up was 2.0 years (range, 2 days to 5.3 years). During a total observation of 3977 patient-years, 130 ischemic and 10 hemorrhagic (5 intraparenchymal, 4 subdural, and 1 subarachnoid) strokes occurred. Of the ischemic strokes, 55% (n=71) were classified as probably cardioembolic, 18% (n=24) as probably noncardioembolic, and the remainder as of uncertain cause. Nearly two thirds (62%) of ischemic strokes were disabling or fatal.

Factors Associated With Ischemic Stroke: Univariate Comparisons

The annualized rate of ischemic stroke was 3.3%/y (95% CI, 2.8 to 3.9) and was higher in those with prior stroke or TIA (n=159; stroke rate=13.0%/y) versus other participants (n=1853; stroke rate=2.7%/y; P<0.001). When we excluded those with prior stroke or TIA, the stroke rate in elderly (ie, aged >75 years) women was substantially higher than that of elderly men (9.7%/y versus 3.2%/y, respectively; P<0.001; Table 2). When we considered all 2012 participants, alcohol use (number of drinks per week) was inversely related to stroke: none=3.8%/y; 1 to 6 per week=3.0%/y; 7 to 13 per week=2.6%/y; and ≥14 per week=1.1%/y (P=0.02). Other factors strongly (P<0.001) associated with stroke by univariate analysis were increased age, hypertension (particularly systolic blood pressure), left ventricular mass index, and left ventricular diastolic dimension (Table 1). Stroke was not significantly associated with a recent history of heart failure (relative risk [RR]=1.7, P=0.09), fractional shortening dichotomized at ≤25% (RR=1.2, P=0.6) or considered as a continuous variable (P=0.9), or moderate to severe left ventricular dysfunction assessed qualitatively by 2-dimensional imaging (RR=1.2, P=0.5), and these associations were not altered by exclusion of those receiving fixed, low-dose warfarin.

Factors Independently Associated With Ischemic Stroke

Six features were significantly and independently associated with ischemic stroke by multivariate analysis (Table 3). Prior stroke or TIA was a powerful independent associate (RR=2.9, P<0.001). To characterize factors independently associated with stroke among participants without prior stroke or TIA (ie, for primary prevention), a separate multi-
variate analysis excluding the 159 participants with prior stroke or TIA was performed, with similar findings (Table 3). Consumption of $14 alcohol-containing drinks per week was associated with a reduced risk of ischemic stroke (Table 3). This effect was not significant with consumption of 7 to 13 drinks per week (adjusted RR = 0.8, $P = 0.6$ compared with nonconsumers). Left ventricular dysfunction, measured in several ways, was not independently associated with stroke in these models.

Two additional variables were collected only in SPAF III participants and were additional independent associates of stroke in participants without prior stroke or TIA ($n = 1073$). After adjustment for other factors independently associated with stroke, including a history of hypertension (Table 3), severity of hypertension provided additional information ($P = 0.04$). Compared with those without hypertension, participants with moderate to severe hypertension had a relative risk of 4.8 ($P < 0.001$), whereas those with hypertension categorized as borderline or mild had a relative risk of 2.3 ($P = 0.02$). The one third of women who used estrogen hormone replacement therapy at SPAF III entry ($n = 90$; mean age, 66 years; 9 ischemic strokes) were on average younger ($P = 0.001$) than those who did not ($n = 184$; mean age, 71 years; 6 ischemic strokes). Estrogen hormone replacement therapy was associated with higher rates of ischemic stroke after adjustment for other independent associates (RR = 3.2, $P = 0.007$). The increased risk associated with hormone replacement therapy was similar for those receiving estrogen alone ($n = 68$) versus estrogen plus progesterone combinations ($n = 19$).

Significant independent associates of disabling/fatal ischemic strokes were similar: prior stroke or TIA (RR = 2.9, $P < 0.001$), systolic blood pressure $> 160 \text{ mm Hg}$ (RR = 2.3, $P = 0.004$), age (RR = 2.0 per decade, $P < 0.001$), history of

| TABLE 1. Clinical and Echocardiographic Features Associated With Ischemic Stroke* |
|-------------------------------|-----------------|-----------------|
| All Participants              | Ischemic Stroke | No Ischemic Stroke |
| Mean±SD age, y                | 69±10           | 74±8§           | 69±10           |
| Women, %                      | 28              | 45§             | 27              |
| Regular alcohol use, %†       | 9               | 3               | 9               |
| Prior stroke or TIA, %        | 8               | 22§             | 7               |
| History of hypertension, %    | 52              | 72§             | 51              |
| Mean±SD systolic BP, mm Hg    | 136±19          | 145±22§         | 135±19          |
| Systolic BP $> 160 \text{ mm Hg}$, % | 10              | 26†             | 8               |
| Cervical bruit or prior CEA, % | 5               | 8               | 5               |
| Peripheral vascular disease, % | 7               | 11              | 6               |
| Mean±SD pulse pressure, mm Hg | 57±17           | 65±20§          | 56±16           |
| Diabetes mellitus, %          | 15              | 22              | 15              |
| Mean±SD LV diastolic dimension, mm | 52±7           | 50±8            | 52±7            |
| Mitral annular calcification, % | 26             | 34              | 25              |
| Moderate to severe mitral annular calcification, % | 7               | 13              | 6               |
| Increased LV mass index‡      | 35              | 51§             | 34              |

BP indicates blood pressure; CEA, carotid endarterectomy; and LV, left ventricular. See Subjects and Methods for complete list of features considered.

*All $P < 0.05$ (2-sided) by univariate analysis.
†$> 14$ drinks per week.
‡$> 110 \text{ g/m}^2$ for women, $> 155 \text{ g/m}^2$ for men.
§$P < 0.001$.

| TABLE 2. Age, Sex, and Stroke in AF: Primary Prevention* |
|-------------------------------|-----------------|-----------------|
| Annualized Rate of Ischemic Stroke |
| Age ≤75 y                      | Age >75 y       | All Ages        |
| (n=1361) (Mean=65 y)           | (n=492) (Mean=80 y) | (n=1853) (Mean=69 y) |
| Women (n=514; mean age, 71 y)  | 2.5%/y          | 9.7%/y          | 4.4%/y          |
| Men (n=1339; mean age, 68 y)   | 1.8%/y          | 3.2%/y          | 2.1%/y          |
| Both (n=1853)                  | 2.0%/y          | 5.2%/y          | 2.7%/y          |

*Univariate (ie, unadjusted) stroke rates among those without prior stroke or TIA. The mean ages of women vs men aged ≤75 years were 66 vs 64, respectively, and aged >75 years were 81 vs 79, respectively.
hypertension (RR = 1.8, P = 0.02), and female sex (RR = 1.8, P = 0.03). In addition, diabetes (RR = 1.9, P = 0.02) was also independently associated with disabling/fatal stroke.

**Stratification of Stroke Risk**

With the use of factors independently associated with ischemic stroke and disabling/fatal ischemic stroke, a risk stratification scheme was generated for participants without prior stroke or TIA (ie, for primary prevention) (Table 4). For this scheme, the novel association of alcohol use ≥14 drinks per week with reduced stroke was not considered, nor was the severity of hypertension or hormone replacement therapy, about which information was available only for SPAF III participants. Participants categorized as low versus moderate versus high risk had significantly different rates of ischemic stroke (0.9%/y, 2.6%/y, 7.1%/y, respectively, P < 0.001) and disabling/fatal ischemic stroke (0.3%/y, 1.6%/y, 5.2%/y, respectively, P < 0.001) (Table 4, Figure 1). Forty-one percent (n = 763) were categorized as low risk and had an observed stroke rate of 0.9%/y (95% CI, 0.6 to 1.6) and a rate of disabling/fatal stroke of 0.3%/y (95% CI, 0.1 to 0.8) (Figure 2). The fractions of ischemic strokes categorized as disabling/fatal were 72%, 60%, and 33% of high-, moderate-, and low-risk patients, respectively.

**TABLE 3. Factors Associated With Ischemic Stroke: Multivariate Analysis**

<table>
<thead>
<tr>
<th>Features</th>
<th>All Participants (n=2012)</th>
<th>Primary Prevention* (n=1853)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted RR</td>
<td>P</td>
</tr>
<tr>
<td>Age (per decade)</td>
<td>1.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.6</td>
<td>0.01</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>2.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic BP &gt;160 mm Hg</td>
<td>2.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alcohol use (≥14/wk)</td>
<td>0.4‡</td>
<td>0.04</td>
</tr>
<tr>
<td>Prior stroke or TIA</td>
<td>2.9</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

NA indicates not applicable.

*Excluding 159 participants with prior stroke or TIA.

†The adjusted RR is 1.4 (P = 0.09) for primary prevention.

‡Compared with those consuming 0–13 drinks per week.

**TABLE 4. Risk Stratification of AF Patients Given Aspirin: Primary Prevention**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Annualized Rate of Ischemic Stroke</th>
<th>Annualized Rate of Disabling/Fatal Ischemic Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥1 Risk Factor</td>
<td>Single Risk Factor</td>
</tr>
<tr>
<td>High risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women &gt;75†</td>
<td>7.9%</td>
<td>7.8%</td>
</tr>
<tr>
<td>Age &gt;75 + history of hypertension</td>
<td>6.9%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Systolic BP &gt;160 mm Hg (any age)</td>
<td>9.6%</td>
<td>7.2%</td>
</tr>
<tr>
<td>All high risk</td>
<td>7.1%‡</td>
<td>(5.4–9.5)</td>
</tr>
<tr>
<td>Moderate risk (no high-risk features)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of hypertension, age ≤75</td>
<td>2.6%</td>
<td>2.6%§</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.9%</td>
<td>2.6%§</td>
</tr>
<tr>
<td>All moderate risk</td>
<td>2.6%‡</td>
<td>(1.9–3.6)</td>
</tr>
<tr>
<td>Low risk (no high- or moderate-risk features)</td>
<td>0.9%‡</td>
<td>(0.6–1.6)</td>
</tr>
</tbody>
</table>

Ranges in parentheses are 95% CI.

*Excludes those with prior stroke or TIA (recent or remote).

†Without hypertension.

§Excluding those assigned combination of low-dose warfarin plus aspirin, stroke rates were 6.4%/y, 2.7%/y, and 1.0%/y for those categorized as high, moderate, and low risk, respectively. Excluding those not taking aspirin for >7 days, stroke rates were 7.0%/y, 2.8%/y, and 0.8%/y for high, moderate, and low risk, respectively.

§For those with both hypertension and diabetes (with no high-risk features), stroke rate was 3.0%/y (n = 130).
low-risk patients, respectively ($P=0.02$, $P=0.009$ for linear association).

Among those categorized as low-risk, age had little influence on stroke rate. The stroke rate for men aged >75 years (n=151) was 1.6%/y (95% CI, 0.7 to 3.9). When we compared those aged 66 to 75 years (n=323) with those aged ≤65 years (n=289), the stroke rates were 1.2%/y versus 0.3%/y, respectively, with no sex-related differences.

Whereas sex had little influence among those aged ≤75 years without risk factors, women had much higher rates of stroke compared with men among those aged >75 years. For participants aged >75 years without hypertension, elevated systolic blood pressure, or prior stroke or TIA, the stroke rate among women (mean age, 81 years) was 7.8%/y (95% CI, 3.7 to 16), significantly exceeding that of men (mean age, 80 years; 1.2%/y; 95% CI, 0.4 to 3.2; $P=0.002$).

The rates of cardioembolic stroke were 0.6%/y, 1.1%/y, and 4.4%/y in low-, moderate-, and high-risk participants, respectively, with corresponding rates of noncardioembolic stroke of 0.2%/y, 0.7%/y, and 0.9%/y. The rate of noncardioembolic stroke was 3 times greater in those at moderate versus low risk (rate ratio=3.5, $P=0.04$) but similar for those at moderate versus high risk.

Among 159 participants with prior stroke or TIA a median of 3.1 years before study entry, the rate of ischemic stroke was 13.0%/y on aspirin. Those with prior stroke or TIA within 12 months of entry had higher stroke rates than those with more remote events ($P<0.001$). Application of the risk stratification scheme (Table 4) to those with prior stroke or TIA showed stroke rates of 20%/y (95% CI, 13 to 32), 10%/y (95% CI, 5.0 to 20), and 5.9%/y (95% CI, 1.9 to 18) among those meeting criteria for high, moderate, and low risk, respectively ($P=0.05$).

When both ischemic strokes and intracranial hemorrhages were considered, the rates of all strokes were 1.1%/y (95% CI, 0.7 to 1.7), 2.7%/y (95% CI, 2.0 to 3.7), and 7.6%/y (95% CI, 5.8 to 10) among those categorized as low, moderate, and high risk, respectively ($P<0.001$) (Figure 1).

**Discussion**

These exploratory analyses of a large number of AF patients given aspirin confirm the link between several previously identified features and ischemic stroke. In addition, regular alcohol consumption and hormone replacement therapy emerged as significantly associated with lower and higher stroke rates, respectively. Left ventricular dysfunction, assessed in several ways, was not independently associated with stroke in this cohort, and consequently, results of precordial echocardiography did not contribute to risk stratification. According to the risk stratification scheme developed here, a substantial fraction (~40%) of this large cohort of AF patients had low rates of ischemic stroke (0.9%/y) and disabling/fatal stroke (0.3%/y) when given aspirin. Most participants aged >75 years were categorized as high risk, while younger participants in this cohort were evenly split between low and moderate risk (Figure 2).

The overall rate of ischemic stroke in this cohort taking aspirin (3.3%/y) was similar to that in other recent studies of AF patients given aspirin,17–19 suggesting that large fractions of younger AF patients given aspirin have low to moderate rates of stroke. On the other hand, AF patients in general medical practice are, on average, older than participants in this cohort, and consequently the fraction at high risk may be larger.20 The effect of aspirin therapy on stroke rates in this cohort cannot be determined in the absence of an untreated, randomized control group. In pooled analysis of randomized trials in AF, aspirin has been associated with a 20% reduction in stroke.1–21 Exploratory analyses of these pooled data suggest that aspirin may be more efficacious for primary prevention,21 for those with hypertension or congestive heart failure,21 and for prevention of noncardioembolic strokes.15 Hence, factors associated with ischemic stroke among untreated AF patients may be different. While aspirin is recognized to accentuate intracranial hemorrhage,22 the rate of primary intracerebral hemorrhage was low in this cohort (~0.1%/y).

Left ventricular systolic dysfunction, indicated by a history of heart failure or by precordial echocardiographic indices, was not associated with ischemic stroke in these patients. The relationship between ventricular dysfunction and stroke in AF patients has varied in recent analyses of this issue. Among placebo-treated participants in the SPAF I study, recent heart failure and left ventricular dysfunction by 2-dimensional echocardiography were both independently associated with stroke.4,5 In a pooled analysis of placebo-treated participants in 5 clinical trials, heart failure was not independently associated with stroke,6 but left ventricular systolic dysfunction by echocardiography was a strong independent associate in 3 of these trials that collected echocardiographic data.23 Previous analysis of SPAF I and II participants taking aspirin showed poor left ventricular function to be independently associated with stroke, particularly in those with additional
risk factors. The use of aspirin by all participants in this analysis may have blunted the association of stroke with ventricular dysfunction. Pathogenetically, left ventricular dysfunction could contribute to formation of left atrial thrombi by augmenting stasis of blood flow in the atrium due to inhibition of passive atrial emptying. If so, ventricular diastolic dysfunction (not well characterized in our study) should theoretically be a better indicator than indices of systolic dysfunction. The contribution of ventricular dysfunction to stroke in AF and to clinical risk stratification requires further study.

Estrogen hormone replacement therapy was independently associated with ischemic stroke in analyses restricted to SPAF III participants (data about hormone replacement therapy were not collected in the earlier SPAF studies). Hormone replacement therapy is known to affect laboratory measures of hemostasis, but the results of studies assessing the clinical effects on stroke are conflicting. Postmenopausal hormone replacement therapy appears to increase the risk of venous thromboembolism. Thorbi forming in the left atrium of AF patients are pathologically closer to venous than arterial thrombi, and the emergence of hormone replacement therapy as independently associated with stroke in patients with AF is intriguing. Additional studies of this issue are needed.

The identification of regular alcohol consumption as independently associated with reduced stroke risk in AF is a novel finding. This could conceivably be an artifact of underreporting or underdetection of minor stroke events in heavy alcohol users. However, moderate alcohol consumption has been associated with a decreased risk of venous thrombosis in older people. At present, whether regular alcohol use affects stroke risk in AF patients remains unclear, and hence this variable is not considered in our risk stratification scheme.

Our results relating stroke to age, hypertension, systolic blood pressure >160 mm Hg, and diabetes in AF patients confirm other studies. Female sex was associated with additional risk of stroke, but only for those aged >75 years. This curious finding was consistent in each of the SPAF trials. This conceivably reflects a particularly high rate of stroke among elderly women with AF, a lack of efficacy of aspirin in these patients, or both. We speculate that elderly women with AF are particularly prone to disabling cardioembolic strokes and derive little benefit from aspirin. The risk stratification scheme was robust for further stratification of stroke risk in those with prior stroke or TIA. However, the rate of ischemic stroke among those with prior stroke or TIA remained significantly higher when adjusted for other variables, suggesting that the factors associated with stroke identified in these analyses do not completely account for the high risk of stroke seen in those with prior events.

Those categorized as moderate risk (ie, diabetics and those aged ≤75 years with hypertension) had the highest proportion of presumed noncardioembolic strokes. The efficacy of adjusted-dose warfarin relative to aspirin for prevention of stroke in AF appears to be greater for cardioembolic infarcts than for noncardioembolic infarcts (although existing clinical classification schemes are imperfect and inadequately validated). Hence, anticoagulation instead of aspirin for this moderate-risk group may not reduce stroke to the same relative extent as for unselected AF patients (=50% reduction in RR) or for high-risk AF patients (=70% reduction in RR). This construct is supported by the results of 2 recent randomized trials, in which the reduction in RR by warfarin over aspirin was modest (=30%) among AF patients, with overall rates of stroke in the range of 2%/y to 3%/y.

Among AF patients taking aspirin, age, hypertension, and prior stroke or TIA were confirmed as independently associated with subsequent ischemic stroke. We regard the specific risk stratification scheme developed here as hypothesis generating, requiring confirmation in a separate cohort of AF patients before it can be applied to clinical management with confidence, since multivariate models tend to overestimate the strength of associations when applied to other cohorts. Our previous SPAF III risk stratification scheme has been prospectively tested and shown to be valid. Another published scheme derived from pooled analysis of placebo-treated patients in several clinical trials, while not separately validated, combined clinical definitions that differed slightly between trials, perhaps enhancing generalizability to clinical practice. More research about the application of risk stratification schemes in AF to clinical practice is needed.

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