Patients With Nonvalvular Atrial Fibrillation at Low Risk of Stroke During Treatment With Aspirin

Stroke Prevention in Atrial Fibrillation III Study

The SPAF III Writing Committee for the Stroke Prevention in Atrial Fibrillation Investigators

Context.—Nonvalvular atrial fibrillation (AF) carries an increased risk for stroke, but absolute rates of stroke vary widely within the broad spectrum of AF patients.

Objective.—To prospectively validate a risk stratification scheme identifying patients with AF with low rates of stroke when given aspirin.

Design.—Prospective cohort study with mean duration of follow-up of 2.0 years, conducted between 1993 and 1997.

Setting.—Outpatient clinics affiliated with academic medical centers.

Patients.—Patients with AF categorized as “low risk” based on the absence of 4 prespecified thromboembolic risk factors: recent congestive heart failure or left ventricular fractional shortening of 25% or less, previous thromboembolism, systolic blood pressure greater than 160 mm Hg, or female sex at age older than 75 years.

Intervention.—All participants given aspirin, 325 mg/d.

Main Outcome Measures.—Ischemic stroke (considered disabling when Rankin score was II or worse 1-3 months later) and systemic embolism (primary events).

Results.—Among 892 participants, the mean (SD) age was 67 (10) years, 78% were men, and histories of hypertension, diabetes, and ischemic heart disease were present in 46%, 13%, and 16%, respectively. The rate of primary events was 2.2% per year (95% confidence interval [CI], 1.6%-3.0%), of ischemic stroke was 2.0% per year (95% CI, 1.5%-2.8%), and of disabling ischemic strokes was 0.8% per year (95% CI, 0.5%-1.3%). Those with a history of hypertension had a higher rate of primary events (3.6% per year) than those with no history of hypertension (1.1% per year) (P<.001). The rate of disabling ischemic stroke was low in those with and without a history of hypertension (1.4% per year and 0.5% per year, respectively). The rate of major bleeding during aspirin therapy was 0.5% per year.

Conclusion.—Patients with AF who have relatively low rates of ischemic stroke, particularly disabling stroke, during treatment with aspirin can be reliably identified.

NEARLY 2 million Americans have nonvalvular atrial fibrillation (AF), a powerful, independent risk factor for ischemic stroke. Several randomized clinical trials have demonstrated that treatment with adjusted-dose warfarin reduces the risk of stroke in AF patients by about two thirds, leading to current recommendations that most AF patients receive lifelong anticoagulation. The efficacy of aspirin for preventing stroke in AF patients is controversial, but supported by pooled results of 3 placebo-controlled trials yielding a 21% reduction in stroke. Although clearly less effective than warfarin therapy for prevention of ischemic events, treatment with aspirin carries a lower risk of bleeding and requires less medical monitoring.

For editorial comment see p 1304.
METHODS

Patients

Eligible patients were adults with AF documented in the 6 preceding months who did not have prosthetic heart valves, mitral stenosis, or other conditions requiring anticoagulation, contraindications to aspirin, or any of 4 specific risk factors for thromboembolism: (1) impaired left ventricular function manifest by recent (within 100 days) congestive heart failure or reduced fractional shortening (25%) by M-mode echocardiography; (2) systolic blood pressure higher than 160 mm Hg at study entry as determined by 2 blood pressure measurements taken on separate days (1 systolic pressure measurement must have exceeded 160 mm Hg and either the other measurement must have exceeded 150 mm Hg or the patient must have had documented systolic blood pressure in the prior 3 months exceeding 160 mm Hg); (3) prior ischemic stroke, transient ischemic attack (TIA), or systemic embolism; or (4) female and older than 75 years.

Blood pressure was measured in the patient’s right arm while sitting after 5 minutes of rest and having had no coffee or tobacco within 1 hour, recording the level of the first Korotkoff sound auscultated during slow deflation of cuff pressure (3 mmHg). Electronically recorded pressures were not allowed. Participants could have a history of hypertension provided that systolic blood pressure was not elevated at the time of screening. Specific criteria for clinical congestive heart failure and echocardiographic measurements have been previously reported. Patients with “lone AF” (ie, age <60 years without clinical cardiovascular disease or hypertension and a normal echocardiogram) were not enrolled; patients with intermittent AF were eligible. Participation required signed informed consent according to federal and local regulations governing research involving human subjects, and the protocol was approved by institutional review boards at each participating site. All participants were assigned to receive enteric-coated aspirin, 325 mg/d (Ecotrin, SmithKline Beecham Consumer Brands, Philadelphia, Pa). Outpatients with AF were recruited from 20 clinical sites in the United States and Canada and were screened at public, private, and Veterans Affairs health care facilities.

We hypothesized that AF patients without any of the 4 thromboembolic risk factors would have a rate of ischemic stroke and systemic emboli (primary events) of less than 3% per year. These thromboembolic risk factors were derived from exploratory multivariate analyses of AF patients receiving aspirin in the Stroke Prevention in Atrial Fibrillation (SPAF) I and II studies. The sample size required to exclude a primary event rate of 3% or higher per year was calculated using a Poisson model to estimate the required patient-years of exposure, as reported in detail elsewhere. Prespecified secondary analyses stratified patients according to the presence or absence of a history of hypertension and considered disability associated with ischemic strokes in the evaluation of outcome events.

Physician investigators evaluated potential patients for thromboembolic risk factors. A history of hypertension was recorded either if the patient was receiving medications for treatment of hypertension or if, based on medical records, blood pressure consistently exceeded 160 mm Hg systolic or 90 mm Hg diastolic during at least 3 months of the year prior to enrollment. Twelve-lead electrocardiography (for the presence of AF) and M-mode and 2-dimensional echocardiography (for left ventricular fractional shortening and index) were carried out at entry and interpreted by study-affiliated cardiologists.

Follow-up

Participants were seen in the clinic at 3 months, 6 months, and every 6 months thereafter and were contacted by telephone between visits at 3-month intervals. At clinic visits, blood pressure was measured, and participants were interviewed to detect ischemic events or development of thromboembolic risk factors. Adherence was assessed by pill count; compliance was categorized as good if 80% or more of the expected number of tablets were taken. Participants were withdrawn from study therapy if any of the 4 thromboembolic risk factors were identified (although all patients were followed up until the end of the study). Subsequent antithrombotic therapy was determined by their personal physicians. For withdrawal from study therapy because of systolic hypertension, blood pressure must have exceeded 160 mm Hg and persisted at least 1 week later.

Outcome Measures

Potential events were detected by interviews with study physicians during clinic visits, by intermittent telephone interviews with research nurses, and by yearly administration of a stroke symptoms questionnaire. All possible strokes, systemic emboli, or TIA were independently verified by consensus of at least 2 members of an events committee, based on the report of a local stroke-affiliated neurologist and review of original medical records from which information about antithrombotic therapy was purged. Events committee members were unaware of whether the patient was in this aspirin-treated cohort or a contemporaneous randomized trial.

Diagnosis of ischemic stroke required focal neurologic symptoms or signs of sudden onset persisting for more than 24 hours. Absence of primary hemorrhage was confirmed by neuroimaging or necropsy in 35 (97%) of 36 patients. When signs and symptoms clinically resolved in 24 hours, a diagnosis of TIA was assigned, even when acute brain infarction was evident by subsequent neuroimag-
Primary events are by intention-to-treat analysis unless otherwise noted. CI indicates confidence interval; CNS, central nervous system; embolism was deemed probable in 2, but these were not included as primary events by protocol stipulation.

Table 2.—Key Outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. of Events</th>
<th>Annualized Rate, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic strokes</td>
<td>36</td>
<td>2.0 (1.5-2.8)</td>
</tr>
<tr>
<td>Non-CNS emboli</td>
<td>3†</td>
<td>. . . ( . . . )</td>
</tr>
<tr>
<td>Total primary events</td>
<td>39</td>
<td>2.2 (1.6-3.0)</td>
</tr>
<tr>
<td>Disabling ischemic strokes‡</td>
<td>14§</td>
<td>0.8 (0.5-1.3)</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>2†</td>
<td>0.1 (0.03-0.5)</td>
</tr>
<tr>
<td>All strokes (ischemic and hemorrhagic)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>38</td>
<td>2.2 (1.6-3.0)</td>
</tr>
<tr>
<td>Disabling†</td>
<td>15</td>
<td>0.9 (0.5-1.4)</td>
</tr>
<tr>
<td>TIA§</td>
<td>23§</td>
<td>1.3 (0.9-2.0)</td>
</tr>
<tr>
<td>All deaths</td>
<td>33</td>
<td>1.8 (1.3-2.6)</td>
</tr>
<tr>
<td>Vascular deaths</td>
<td>19</td>
<td>1.0 (0.7-1.6)</td>
</tr>
<tr>
<td>Stroke, myocardial infarction, or vascular death</td>
<td>62</td>
<td>3.5 (2.8-4.5)</td>
</tr>
<tr>
<td>Develop high-risk features</td>
<td>106</td>
<td>6.5 (5.4-7.9)</td>
</tr>
<tr>
<td>Primary events while “low risk”§</td>
<td>37</td>
<td>2.3 (1.7-3.1)</td>
</tr>
<tr>
<td>Major non-CNS hemorrhage‡</td>
<td>11**</td>
<td>0.6 (0.3-1.1)</td>
</tr>
</tbody>
</table>

Based on 892 participants with a total period of observation of 1814 years, 1763.7 for primary event, all rates are by intention-to-treat analysis unless otherwise noted. CI indicates confidence interval; CNS, central nervous system; TIA, transient ischemic attack. Ellipses indicate data not applicable.

†Three additional participants had obstruction of cranial arteries associated with atherosclerotic peripheral vascular disease: embolism was deemed probable in 2, but these were not included as primary events by protocol stipulation.
‡Disabling strokes were Rankin score of II or worse 1 to 3 months later.
§Six were Rankin score of II; none was fatal.
One immediately followed fibrinolytic therapy given for acute myocardial infarction.
Two had evidence of brain infarction by neuroimaging despite resolution of symptoms and signs within 24 hours.
Follow-up censored at the time “high-risk” features were identified.
Four of 11 were receiving warfarin at the time of bleeding.

**Based on 892 participants with a total period of observation of 1814 years, 1763.7 for primary event, all rates are by intention-to-treat analysis unless otherwise noted. CI indicates confidence interval; CNS, central nervous system; and TIA, transient ischemic attack. Ellipses indicate data not applicable.**

A neurologist assessed all patients with stroke 1 to 3 months after the event to evaluate residual disability. Strokes were judged disabling when the modified Rankin score was II (corresponding to restriction in lifestyle that did not prevent living independently) or worse. A diagnosis of systemic embolism was made when there was abrupt vascular insufficiency related to arterial occlusion without previous evidence of atherosclerosis. When sudden vascular occlusion occurred in a limb affected by atheroembolism, it was categorized as “possibly embolic” if clinical and radiographic features were suggestive of embolic obstruction, but was not counted as a primary event. Major hemorrhage was assessed by the criteria of Landefeld et al. Statistical Analysis

All reported analyses were prespecified, except an exploratory multivariate analysis to identify features associated with primary events during follow-up. This analysis used a forward stepwise procedure with $P = .05$ to enter the model. A safety committee not involved in the conduct of the study monitored primary events for unexpectedly high rates. Analyses were intent to treat where noted. Confidence intervals for event rates were computed using a Poisson distribution. Time to event was computed using product-limit estimates, and Cox proportional hazards models were used to develop multivariate models related to events. Model assumptions were verified by inspection of survival curves. For some secondary analyses, follow-up was censored at the time thromboembolic risk factors were identified by the study investigators. Comparisons of baseline characteristics between groups used the $t$ test for categorical variables and the Student $t$ test for continuous variables. All tests were 2-sided, and significance was accepted at the $P = .05$ level.

RESULTS

A total of 892 participants were enrolled between May 1993 and November 1996 at 20 clinical centers in the United States and Canada. Their mean (SD) age was 67 (10) years; 78% were men; and histories of hypertension, diabetes, and ischemic heart disease were present in 46%, 13%, and 16%, respectively (Table 1). Medical contraindications to warfarin anticoagulation were present in 2%, while 33% were receiving warfarin prior to enrollment (stopped at study entry). The mean (SD) estimated duration of AF was 7 (9) years (median, 4 years).

Participants were followed up for a mean of 2.0 years (range, 3 months to 3.9 years); no patients were lost to follow-up. Compliance with aspirin was categorized as good for 86% of follow-up intervals. Risk factors for thromboembolism developed at a rate of 5.5% per year, including congestive heart failure at 3.2% per year, systolic hypertension at 1.4% per year, women reaching the age of 70 years at 0.6% per year, and TIA at 1.4% per year. Other reasons for withdrawal from active status occurred at a rate of 3.9% per year, including participant request (0.4% per year). The rate of primary events was 2.2% per year (95% confidence interval [CI], 1.6%-3.0%) with no appreciable change in rate during 3 years of follow-up (Table 1, Figure). The rate of ischemic stroke was 2.0% per year (95% CI, 1.5%-2.8%), and the rate of disabling ischemic stroke was 0.8% per year (95% CI, 0.5%-1.3%). Transient ischemic attacks occurred at a rate of 1.3% per year; in 2 of 23 patients with clinical TIA, neuroimaging studies suggested acute brain infarction. The primary event rate was essentially unchanged when follow-up was censored at the time any of the 4 prespecified thromboembolic risk factors were identified (Table 2). Strokes were categorized as probably cardioembolic in 50%, probably noncardioembolic in 25%, and uncertain etiology in 25%, based on neurologic features.

The rate of primary events among those with a history of hypertension (46% of the cohort) was significantly higher than for remaining participants (3.6% [95% CI, 2.5%-5.2%] vs 1.1% [95% CI, 0.6%-2.0%] per year; $P <.001$). The rate of disabling ischemic strokes was also higher for those with vs those without a history of hypertension (1.4% [95% CI, 0.8%-2.6%] vs 0.5% [95% CI, 0.2%-1.2%] per year, respectively; $P = .05$). Multivariate analysis confirmed that a history of hypertension was an independent predictor of primary events (relative risk [RR], 3.3; 95% CI, 1.7-6.9; $P = .001$); age was the only other statistically significant predictor (RR increase of 1.7 per 10 years; 95% CI, 1.1-2.6; $P = .01$) in the multivariate model. Other features included in the multivariate model that were not significant predictors were sex, women aged 70 to 75 years, diabetes, ischemic heart disease, remote history of heart failure, current tobacco smoking, blood pressure at entry and during follow-up.
up, fractional shortening of 20% to 30%, left ventricular muscle mass, and left atrial diameter greater than 5.0 cm. Major bleeding occurred in 13 patients (0.7% per year). Of 11 non–central nervous system (CNS) hemorrhages, 4 occurred while patients were receiving warfarin following withdrawal from aspirin therapy. The rate of non-CNS major bleeding in patients receiving aspirin was 0.4% per year (6 of 7 gastrointestinal hemorrhages).

COMMENT

These results suggest that patients with AF can be prospectively identified who have a low risk of stroke, particularly disabling ischemic stroke, when taking aspirin. Such patients may not benefit substantially from treatment with warfarin, since their rate of stroke during aspirin therapy is sufficiently low that warfarin could only minimally reduce the absolute rate of stroke. For those AF patients without a history of hypertension or any of the 4 specific risk factors, the rate of ischemic stroke approximated that of the general population of this age range, about 1% per year. In contrast, AF patients with 1 or more of the 4 thromboembolic risk factors who entered a separate randomized trial component of the SPAF III Study had much higher rates of stroke (averaging 8% per year), even when treated with aspirin in combination with low doses of warfarin. These clinical criteria, applied by nearly 40 study-affiliated physicians at 20 clinical sites, distinguished AF patients with high rates of thromboembolism from those at lower risk, and the stratification appeared durable over 2 to 3 years. Using these criteria, a large fraction of AF patients could be identified who have low to moderate risks of stroke if treated with aspirin alone—about half the participants in earlier SPAF studies and a similar proportion of a population-based cohort of people with AF (Robert G. Hart, MD, for the Cardiovascular Health Study Investigators, unpublished data, March 1998).

Whether aspirin therapy contributed to the low event rates observed in this study cannot be determined in the absence of an untreated control group. Pooled analysis of 3 randomized trials testing aspirin in AF patients suggests an overall 21% reduction in stroke. While the rate of major hemorrhage associated with daily use of aspirin in these trials (75-325 mg/d) was similar to that with placebo, other larger studies suggest that even low doses of aspirin slightly increase the rate of major hemorrhage. Because of the low rates of stroke and major hemorrhage observed in this cohort, direct comparison of aspirin therapy with either warfarin or placebo in randomized trials would require many thousands of participants and could demonstrate only small differences, unlikely to be clinically important.

The relative benefits and risks afforded by aspirin vs placebo or adjusted-dose warfarin were not assessed directly by this study, as all participants received aspirin. Based on other placebo-controlled studies, however, it can be estimated that for every 1000 AF patients without any of the 4 specific risk factors, about 5 ischemic strokes would be prevented and about 3 major hemorrhages would occur each year among those treated with aspirin. In a low-risk cohort of AF patients defined by our criteria, warfarin treatment instead of aspirin would prevent about 10 ischemic strokes and cause perhaps 10 to 12 major hemorrhages for every 1000 patients per year. By comparison, among high-risk AF patients (with 1 or more risk factors), about 60 ischemic strokes would be prevented by using warfarin instead of aspirin for every 1000 treated for 1 year. These estimates, derived from previous clinical trials, are subject to controversy, particularly those surrounding bleeding rates during anticoagulation in clinical trials vs clinical practice.

The definitions of stroke and systemic embolism were those used in the previous SPAF trials and similar to other recent studies. Other vascular events that did not meet these criteria may still be clinically relevant, including TIAs with evidence of acute cerebral infarction by neuroimaging and acute leg artery occlusions in patients with arteriosclerosis. When these events were included, the rate of events was 2.4% per year. On the other hand, the rate of disabling ischemic stroke, even when those resulting in minimal restriction of lifestyle (Rankin score of II) were considered, was relatively low (0.8% per year). In this cohort of AF patients with a low risk of stroke, disabling stroke represented a majority of thromboembolic events, while it comprises a majority of strokes in unselected and high-risk AF populations. These nondisabling strokes cannot be considered trivial events, but the risk-benefit assessment of antithrombotic options for stroke prevention should consider stroke severity. Patients with a history of hypertension had a significantly higher rate of ischemic stroke than those without hypertension in a prespecified secondary analysis prompted by earlier analyses of patients receiving aspirin in the SPAF I and II studies. Hypertension has been consistently associated with stroke risk in AF patients and appears to be associated with an increased risk for cardioembolic stroke in AF patients. While the rate of stroke remained higher for those with a history of hypertension, subgroup analysis of pooled data from 3 randomized trials suggests that aspirin is efficacious for AF patients with a history of hypertension. It is unknown whether sustained control of hypertension reduces the rate of thromboembolism in AF to that approaching the rate in AF patients without hypertension. The independent influence of patient age on stroke risk in these relatively low-risk AF patients disclosed by the exploratory multivariate analysis supports the findings of others and merits additional investigation. Age was not a prespecified risk factor, based on lack of independent predictive value in the derivation data set, and hence we are less confident of its reliability.

It may be clinically useful to stratify AF patients into 3 levels of risk based on our criteria: low (about 1.0% per year) for those without thromboembolic risk factors or hypertension, moderate (about 3.5% per year) for those with a history of hypertension but no other risk factors, and high (about 8% per year) for those with risk factors unless treated with anticoagulation. Whether AF patients at moderate risk of ischemic stroke while receiving aspirin would importantly benefit from adjusted-dose warfarin should take into account patient values and preferences as well as the safety of anticoagulation vs aspirin therapy for the individual patient.

Thromboembolic risk factors were identified during follow-up in 6% per year of participants who were deemed free of them initially, and periodic reassessment to detect thromboembolic risk factors that favor the use of warfarin is important to minimize stroke.

A substantial fraction of the patients with AF, identifiable by specific clinical criteria, have low rates of thromboembolism during aspirin therapy and benefit much less from anticoagulation than would high-risk AF patients. Additional studies of larger cohorts may clarify pathogenic links and refine risk stratification in the future. Furthermore, results of treatment of patients in clinical practice may vary from those in research trials and studies, and additional studies of the application of these criteria in clinical practice would be welcome. To provide optimum patient safety, selection of antithrombotic prophylaxis for AF patients should consider the widely different rates of thromboembolism associated with individual patient features.

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