Stroke Prevention in Atrial Fibrillation Study
Final Results

Stroke Prevention in Atrial Fibrillation Investigators*

Background. Atrial fibrillation in the absence of rheumatic valvular disease is associated with a fivefold to sevenfold increased risk of ischemic stroke.

Methods and Main Results. The Stroke Prevention in Atrial Fibrillation Study, a multicenter, randomized trial, compared 325 mg/day aspirin (double-blind) or warfarin with placebo for prevention of ischemic stroke and systemic embolism (primary events), and included 1,330 inpatients and outpatients with constant or intermittent atrial fibrillation. During a mean follow-up of 1.3 years, the rate of primary events in patients assigned to placebo was 6.3% per year and was reduced by 42% in those assigned to aspirin (3.6% per year; p=0.02; 95% confidence interval, 9–63%). In the subgroup of warfarin-eligible patients (most less than 76 years old), warfarin dose-adjusted to prolong prothrombin time to 1.3-fold to 1.8-fold that of control reduced the risk of primary events by 67% (warfarin versus placebo, 2.3% versus 7.4% per year; p=0.01; 95% confidence interval, 27–85%). Primary events or death were reduced 58% (p=0.01) by warfarin and 32% (p=0.02) by aspirin. The risk of significant bleeding was 1.5%, 1.4%, and 1.6% per year in patients assigned to warfarin, aspirin, and placebo, respectively.

Conclusions. Aspirin and warfarin are both effective in reducing ischemic stroke and systemic embolism in patients with atrial fibrillation. Because warfarin-eligible patients composed a subset of all aspirin-eligible patients, the magnitude of reduction in events by warfarin versus aspirin cannot be compared. Too few events occurred in warfarin-eligible patients to directly assess the relative benefit of aspirin compared with warfarin, and the trial is continuing to address this issue. Patients with nonrheumatic atrial fibrillation who can safely take either aspirin or warfarin should receive prophylactic antithrombotic therapy to reduce the risk of stroke. (Circulation 1991;84:527–539)

By the late 1970s, it had become clear that atrial fibrillation in the absence of rheumatic valvular disease is associated with an increased risk of ischemic stroke.1–3 The pathogenesis of these strokes is uncertain and probably multifactorial, but a substantial portion is probably a result of cardiogenic embolism, whereas others are caused by associated intrinsic cerebrovascular diseases. Atrial fibrillation predisposes to the formation of left atrial thrombi, which can embolize,4,5 and antithrombotic medication has been proposed for stroke prevention.

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In 1985, cardiologists and neurologists from several institutions jointly designed the Study Prevention in Atrial Fibrillation (SPAF) Study to determine the efficacy and safety of warfarin and aspirin compared with placebo for the prevention of ischemic stroke and systemic embolism.6 After a pilot study, funding was obtained, and the SPAF investigators began enrolling patients in June 1987. The placebo arm was terminated in late 1989 when the superiority of both warfarin and aspirin relative to placebo was established. The preliminary results describing the effect of active antithrombotic therapy (aspirin or warfarin) versus placebo in 1,244 patients have been published.7 We now report our final results in the entire population of 1,330 patients and describe the individual efficacies of aspirin and warfarin.

Methods

The SPAF Study was a randomized clinical trial carried out at 15 centers. Adjusted-dose warfarin and aspirin (given separately) were compared with placebo for the prevention of ischemic strokes and systemic emboli (primary events) in patients with nonrheumatic atrial fibrillation. The specific objectives, general design, and statistical aspects have been reported previously6,7; we summarize key features and relevant specific criteria. These final results

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Address for correspondence: Ruth McBride, Statistics and Epidemiology Research Corporation, 1107 NE 45th Street, Suite 520, Seattle, WA 98105.

Participating investigators are listed in "Appendix 1."

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include the 1,244 patients described in our preliminary report\(^7\) plus 86 additional patients subsequently randomized before the termination of the placebo arms.

Eligible patients were adults with electrocardiographic documentation of atrial fibrillation in the preceding 12 months without prosthetic heart valves, echocardiographic evidence of mitral stenosis, and other requirements for or contraindications to aspirin or warfarin therapy (exclusion criteria are listed in Table 1). Patients with a history of stroke or transient ischemic attack (TIA) more than 2 years before entry were eligible; therefore, although SPAF is in large part a primary prevention trial, 7% of enrolled patients had a history of prior clinical brain ischemia. Potential participants were identified as inpatients or outpatients from public, private, and Veterans Administration health-care facilities by review of electrocardiographic logs, by direct referral from participating and nonparticipating physicians, and by self-referral in response to notices in various media. Eligible, consenting patients were categorized (Figure 1) as warfarin eligible (group 1) or warfarin ineligible (group 2) based on specific criteria that included the unwillingness of certain patients or their physicians to accept warfarin therapy, circumstances associated with excessive hemorrhagic risk, and the low incidence of embolism in cases of isolated atrial fibrillation without other evidence of cardiovascular disease (Table 2). During most of the enrollment period, age of more than 75 years mandated warfarin ineligibility because of fear of excess risk of hemorrhage; based on our early experience and that of another recent trial,\(^8\) this age restriction was elimi-
nated in November 1988. Given this study design (Figure 1), warfarin would be compared with placebo in warfarin-eligible patients only (group 1), and all patients receiving aspirin would be compared with all patients receiving placebo (groups 1 and 2 combined). Our primary objectives were to determine whether aspirin was of benefit in all eligible patients and whether warfarin was of benefit in the subset of patients who could and would take warfarin. Predicted event rates, sample size estimates, and monitoring bounds have been previously reported. A direct comparison of warfarin with aspirin was not a goal of this initial phase because we were not certain that either was effective, and sample size was insufficient to address this question. Such a comparison is the focus of the ongoing SPAF II Study, which includes the patients treated with aspirin in the warfarin-eligible group of this study; therefore, the data on aspirin versus warfarin in group 1 are not presented separately in the present analysis.

Group 1 patients had an equal chance of assignment to open-label warfarin (Coumadin®, du Pont, Wilmington, Del.), aspirin in a double-blind fashion, or matched placebo in a double-blind fashion. The dose of warfarin was adjusted to prolong the prothrombin time using conventional North American rabbit brain thromboplastin reagents between 1.3-fold and 1.8-fold that of control (approximate International Normalized Ratio, 2.0–4.5). Patients in group 2 received either aspirin or placebo in a double-blind fashion. In both group 1 and group 2, the aspirin dose was 325 mg/day (enteric-coated aspirin, Ecotrin®, SmithKline-Beecham, Philadelphia). All patients underwent M-mode and two-dimensional echocardiography within 3 months before entry. Echocardiograms were interpreted locally, and a videotape copy was sent to a central echocardiographic registry. All of the patients were followed every 3 months to detect complications of drug therapy (particularly hemorrhagic events) as well as the development of primary (ischemic stroke or systemic embolism) or secondary events (death, myocardial infarction, TIA, or unstable angina pectoris requiring hospital admission) (see definitions in “Appendix 2”)

### Table 2. Criteria for Ineligibility for Anticoagulant Therapy and Assignment to Group 2

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Ineligible patients (n)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient or attending physician refused anticoagulant therapy</td>
<td>239</td>
</tr>
<tr>
<td>Age of more than 75 years†</td>
<td>173</td>
</tr>
<tr>
<td>Inability to obtain adequate follow-up for prothrombin time monitoring</td>
<td>57</td>
</tr>
<tr>
<td>Lone atrial fibrillation complex‡</td>
<td>56</td>
</tr>
<tr>
<td>Repeated falls or unstable gait predisposing to head trauma</td>
<td>43</td>
</tr>
<tr>
<td>Positive stool test for occult blood</td>
<td>26</td>
</tr>
<tr>
<td>Chronic alcohol habituation</td>
<td>22</td>
</tr>
<tr>
<td>Gastrointestinal or genitourinary bleeding in preceding 6 months</td>
<td>19</td>
</tr>
<tr>
<td>Uncontrolled hypertension§</td>
<td>18</td>
</tr>
<tr>
<td>Occupational hazards to anticoagulant therapy</td>
<td>18</td>
</tr>
<tr>
<td>Severe hemorrhage during previous anticoagulant therapy despite therapeutic prothrombin time</td>
<td>11</td>
</tr>
<tr>
<td>Recurrent syncope or uncontrolled seizure disorder</td>
<td>10</td>
</tr>
<tr>
<td>Intrinsic prolongation of prothrombin time more than 2 seconds beyond control value on two occasions</td>
<td>8</td>
</tr>
<tr>
<td>Previous intracranial hemorrhage</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>703</td>
</tr>
</tbody>
</table>

*Values indicate the number of patients excluded from group 1 and assigned to group 2 for each reason. For each patient, only the primary reason for exclusion is given.
†This criterion was abandoned by a consensus of the study's steering committee in November 1988.
‡Diagnosis required all of the following: age of 50 years or less, echocardiographic left atrial size of 2.1 cm or less per square meter of body surface area, and no associated cardiopulmonary disease except mitral valve prolapse.
§Diagnosis required systolic blood pressure of more than 180 mm Hg or diastolic pressure of more than 100 mm Hg despite antihypertensive therapy.
ical centers. Original medical records were then submitted and edited to exclude reference to treatment before verification by the Events Committee, the members of which were thus unaware of treatment allocation.

All of the analyses (except where otherwise specified) were based on an intention-to-treat premise. Baseline comparisons between patient characteristics were performed with a $\chi^2$ test for categorical data and a $t$ test for continuous data. Comparisons of treatments for both primary and secondary events used the log-rank test for time to event. Ninety-five percent confidence intervals were calculated on the basis of the relative risk.\textsuperscript{10} Event rates were computed using the Kaplan-Meier\textsuperscript{11} method.

**Results**

**Patient Population and Characteristics**

During 30 months of recruitment, 1,269 patients were entered and an additional 61 patients from the pilot study were continued on protocol. Of 1,330 total randomized patients, 627 (47%) were assigned to group 1 (warfarin eligible) and the remaining 703 were assigned to group 2 (warfarin ineligible) (Figure 1). Patients were recruited from review of inpatient (18%) and outpatient (15%) electrocardiographic logs, by direct referral of patients by study-affiliated and other physicians (46%), by self-referral in response to advertisement (5%), from cardiology Holter monitoring and echocardiography laboratories (6%), and from other sources (10%). Common reasons for exclusion included refusal by the patient or their personal physician to enter a placebo-controlled study (11%): recent stroke, TIA, or systemic embolism (10%); prosthetic cardiac valve (9%); recent myocardial infarction, coronary bypass surgery, or angioplasty (5%); and transient, self-limited atrial fibrillation (6%) (Table 1). Patients were deemed ineligible for anticoagulation because of the patient's or attending physician's refusal (34%), age of more than 75 years at enrollment (25%), inability to obtain adequate follow-up for prothrombin time monitoring (8%), lone atrial fibrillation complex (8%), and other medical contraindications (Table 2). The characteristics of a sample ($n=132$) of otherwise eligible patients who refused entry were not significantly different from those of a concurrent group of patients entering the trial.

Randomized patients had a mean age of 67 years, 71% were men, and approximately half (52%) had a history of hypertension (Table 3). The percentage of women (29% overall) was 39% when patients from Veterans Administration facilities ($n=359$, 27%) were excluded. Most patients had constant atrial fibrillation (66%) of more than 1 year's duration (68%). Definite angina pectoris was present in 10%, and definite prior myocardial infarction was present in 8% of patients. Based on local interpretation, 26% had a left atrial diameter exceeding 5.0 cm by M-mode echocardiography, and 12% had moderate-to-severe ventricular dysfunction by two-dimensional echocardiographic measurements. Of the 1,330 patients enrolled, 84% were Caucasian, 6% were black, and 10% were Asian, Hispanic, or other. The mean±SD duration of atrial fibrillation at entry was 4.9±7.1 years (median duration, 2.1 years). The spectrum of clinical features varied with age, sex, and dysrhythmia pattern (Table 3). Women were an average of 4 years older than men but otherwise had no important differences in clinical characteristics. Patients classified at entry as having constant atrial fibrillation ("Appendix 2") were older with a longer duration of the dysrhythmia and a substantially larger left atrial size compared with those with intermittent atrial fibrillation (Table 3). Randomization resulted in an equal distribution of clinical variables with no significant differences between treatment assignments (Table 4).

**Execution**

Of 7,050 scheduled follow-up visits, 98.5% were completed. No patients were lost to follow-up. Compliance in patients randomized to aspirin or placebo was assessed by interview and pill counts at each follow-up contact. Patients reported interruption in therapy at 14% of follow-up visits for a mean of 20 days. Including these reported interruptions, 88% of patients averaged more than 80% compliance by pill count during the study. In patients assigned to warfarin, 87% of 2,597 expected monthly prothrombin times were recorded. The mean±SD dosage of warfarin was 4.8±1.9 mg/day. The prothrombin time ratio averaged 1.45±0.23 with 71% of all values falling within the target range of 1.3–1.8, 5% above the range, and 23% below the range.

Patients were withdrawn from therapy for the occurrence of secondary events (e.g., myocardial infarction, unstable angina, and TIA) or the development of exclusion criteria (coronary artery bypass surgery, angioplasty, venous thrombosis, and prosthetic valve replacement) that required antithrombotic therapy (Table 5). Withdrawals of medication for reasons unrelated to end point events occurred at a rate of 11.2%, 5.0%, and 6.6% in patients assigned to warfarin, aspirin, and placebo, respectively. The aspirin and placebo blind was not broken routinely for withdrawn patients, so several patients assigned to aspirin were withdrawn to receive aspirin after a secondary event; 25% of those withdrawn from aspirin were subsequently treated with aspirin in various dosages (Table 5).

During the course of the trial, unblinding was known to occur in 10 of 1,120 patients (0.9%) assigned to aspirin or placebo for optimal management of primary and secondary events. Blinding was effective, as assessed by questioning of patients and investigators at study exit showing no predictive value for their best guess of therapy assignment.
### Treatment Outcomes: Warfarin Versus Placebo

The rate of ischemic stroke and systemic embolism was substantially reduced in those assigned to warfarin (2.3% per year) compared with placebo (7.4% per year) \(p=0.01\); risk reduction, 67%; 95% confidence interval, 27–85%) (Table 6 and Figure 2). The risk of a primary event or death was reduced by 58% \(p=0.01\); 95% confidence interval, 20–78%) in those assigned to warfarin. Considering only disabling ischemic strokes or vascular deaths, patients assigned to warfarin had a 54% reduction compared with placebo (five versus 11, \(p=0.11\)).

Of six ischemic strokes in patients assigned to warfarin, only two had therapeutic prothrombin times (prothrombin time ratios, 1.3 and 1.7) at the time of stroke. Two patients had previously been withdrawn from warfarin, and two others had stopped receiving warfarin 5 days before stroke and had normal prothrombin times.

### Treatment Outcomes: Aspirin Versus Placebo

In all patients (groups 1 and 2 combined) assigned to aspirin, there was a lower rate of primary events (3.6% per year) than in those given placebo (6.3% per year) \(p=0.02\); risk reduction, 42%; 95% confidence interval, 9–63%) (Table 7 and Figure 3). The reduction in primary events or death was 32% \(p=0.02\); 95% confidence interval, 7–50%). Considering ischemic strokes, TIAs, and systemic emboli in this double-blinded portion of the SPAF Study, risk reduction was 44% \(p<0.01\); 95% confidence interval, 17–62%). Disabling ischemic stroke or vascular death was reduced by 22% \(p=0.33\) in patients assigned to aspirin relative to placebo therapy.

Of 26 primary events in patients assigned to aspirin, 22 had taken aspirin within 7 days of the event, two had previously been withdrawn, and two were noncompliant. Of 46 primary events in placebo-assigned patients, one was receiving aspirin and one...
was receiving another antiplatelet-aggregating agent at the time of the event. Of 78 total primary events, 71 (91%) were ischemic strokes; of seven systemic emboli, five involved the lower extremities, and one each involved an upper extremity and the kidney. Of the 71 patients who experienced an ischemic stroke in all treatment arms, all had computed tomography in the acute phase, an autopsy, or, in one patient, cerebral arteriography confirming the ischemic etiology. Both intracranial hemorrhages were confirmed by computed tomography.

**Major Complications**

Major complications consisted of bleeding episodes with overall rates between 1% and 2% per year in the treatment arms (Table 8). Of six total central nervous system hemorrhages, two were fatal primary intracerebral hemorrhages (one each in patients assigned to warfarin and to aspirin), and four were subdural hematomas (three with full recovery). Most bleeding episodes that met the criteria for major complications were successfully managed without sequelae. The rate of major complications with sequelae was less than 1% per year in all treatment arms (Table 8). Efficacy-type analysis limited to hemorrhages occurring within 14 days of receiving the assigned medication and unrelated to major precipitating events (e.g., blood transfusions required at the time of coronary artery bypass surgery or with surgical repair of hip fracture) showed risk of relevant hemorrhage of 1.2% per year in patients initially assigned to warfarin.

**Discussion**

The primary analyses of this multicenter, randomized clinical trial demonstrate that both warfarin and aspirin (given separately) reduce the risk of ischemic stroke and systemic embolism in patients with non-
TABLE 5. Withdrawals From Assigned Therapy

<table>
<thead>
<tr>
<th>Reasons for withdrawal (n)</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Aspirin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total withdrawn patients (n)</td>
<td>40</td>
<td>29</td>
<td>63</td>
<td>86</td>
</tr>
<tr>
<td>Mean time to withdrawal (days)</td>
<td>254</td>
<td>288</td>
<td>310</td>
<td>280</td>
</tr>
</tbody>
</table>

**Secondary events***: Warfarin (n=210) Placebo (n=211) 8 8 20 30

**Exclusion criteria***: Warfarin (n=210) Placebo (n=211) 7 8 12 21

**Major complication***: Warfarin (n=210) Placebo (n=211) 3 3 7 8

**Medication intolerance**: Warfarin (n=210) Placebo (n=211) 4 1 0 2

**Abdominal symptoms**: Warfarin (n=210) Placebo (n=211) 0 0 0 2

**Other**: Warfarin (n=210) Placebo (n=211) 1 1 5 4

**Poor compliance or patient request**: Warfarin (n=210) Placebo (n=211) 17 8 20 19

**Subsequent therapy**: Warfarin (n=210) Placebo (n=211) 10 7 16 22

Warfarin (n=552) Placebo (n=568) 5 9 8 17

*Secondary events (transient ischemic attack, myocardial infarction, unstable angina) and certain exclusion criteria (prosthetic valve replacement, coronary artery bypass surgery or angioplasty, venous thrombosis) required withdrawal because of the perceived need for active antithrombotic therapy.**

†See Table 8 for specific details.

rheumatic atrial fibrillation. In the dosages used in this protocol, both antithrombotic therapies were well tolerated and relatively safe. In patients assigned to warfarin versus placebo, the magnitude of the absolute reduction in all ischemic strokes and systemic emboli (5.1% per year) and in the subset of moderate-to-severe strokes (2.1% per year) more than offset the incremental increase (0.8% per year)

TABLE 6. Primary and Secondary Events: Warfarin Versus Placebo

<table>
<thead>
<tr>
<th>Event</th>
<th>Warfarin (n=210)</th>
<th>Placebo (n=211)</th>
<th>Risk reduction*</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic stroke (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimally disabling</td>
<td>4</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderately to severely disabling</td>
<td>2</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic embolism (n)</td>
<td>0</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total primary events (n)</strong></td>
<td>6 (2.3%/yr)</td>
<td>18 (7.4%/yr)</td>
<td>0.67 (0.27–0.85)</td>
<td>0.01</td>
</tr>
<tr>
<td>Intracerebral hemorrhage (n)</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transient ischemic attack without primary events (n)</td>
<td>3 (1.1%/yr)</td>
<td>4 (1.6%/yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q wave</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Q wave</td>
<td>0</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncertain</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total myocardial infarction (n)</strong></td>
<td>2 (0.8%/yr)</td>
<td>2 (0.8%/yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cause of death (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular</td>
<td>3</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probable vascular</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonvascular</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indeterminant</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total mortality (n)</strong></td>
<td>6 (2.2%/yr)</td>
<td>8 (3.1%/yr)</td>
<td>0.25 (−1.11–0.73)</td>
<td>0.56</td>
</tr>
<tr>
<td>Primary event or death (n)</td>
<td>10 (3.8%/yr)</td>
<td>24 (9.8%/yr)</td>
<td>0.58 (0.20–0.78)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Total patient-years of observation†</strong></td>
<td>260</td>
<td>244</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Risk reduction was calculated as 1 minus the relative risk. Values in parentheses are 95% confidence intervals. Some risk reduction values and some lower bounds for the 95% confidence intervals are less than zero, indicating a potential increase in risk. Event rates were based on patient-years of exposure, which varied slightly for each event.†Patient-years are given for the primary end point. Patient-years of exposure for other end points varied slightly.
in major hemorrhage attributed to antithrombotic therapy (Tables 6 and 8). We were unable to define the relative value of aspirin compared with warfarin because too few events occurred in the warfarin and aspirin arms of group 1 to allow meaningful direct comparison. Indirect comparison of the magnitude of reduction in primary events in those assigned to warfarin (67%) versus all patients (groups 1 and 2 combined) assigned to aspirin (42%) may be misleading. Warfarin-ineligible patients (group 2) were included in the aspirin comparison, and their response to aspirin might not have been identical to that of warfarin-eligible patients who were assigned to aspirin (i.e., group 1 alone). Subgroup analysis based on group 1 versus group 2 classification, age, and other factors suggests that the beneficial effect of aspirin may not be uniform but such secondary analyses require further characterization and confirmation. The SPAF Study was halted at the second interim analysis after a mean of 1.3 years of follow-up because aspirin, warfarin, or both independently in group 1 patients crossed a group sequential boundary (requiring $p<0.003$) for reduction in primary events.6,7,12 As in our preliminary report,7 results are not reported comparing aspirin with warfarin in group 1 because no statistically significant difference existed with the small number of events. The SPAF Study is continuing to compare these therapies directly in warfarin-eligible patients of all ages over a longer follow-up period.

Because of our screening techniques, many patients with atrial fibrillation were identified who did not enter the trial because of either ineligibility or refusal. Several reasons for exclusion had in common a perceived requirement for antithrombotic therapy (i.e., placebo treatment unacceptable) such as recent myocardial infarction, stroke, unstable angina, prosthetic cardiac valves, and so on. We believe that our results are generalizable to the substantial proportion of excluded patients who were eligible but refused entry, because their clinical features were very similar to those of patients who entered the trial. The characteristics of the 1,330 patients who enrolled in the SPAF Study reflect the broad spectrum of patients with atrial fibrillation seen by many physicians for whom the need for antithrombotic prophylaxis was previously unclear.13,14

There are several possible ways to record and report complications of antithrombotic therapy, each with advantages and disadvantages. Clinicians compare complication rates with treatment benefits to assess overall therapeutic value. How many gastrointestinal hemorrhages requiring blood transfusion but having full recovery offset a minor stroke? We have chosen to report complications as all major hemorrhages, major hemorrhage with residua, and hemorrhage relevant to therapy to allow different comparisons. By any criteria, the major hemorrhage rate was low in this population treated by our protocol, favoring the use of antithrombotic therapy in all except the very lowest-risk patients.15 Patients were carefully selected for anticoagulation and were followed closely, contributing to the relatively low rates of major bleeding found in this trial. Because of the protocol specifications, patients more than 75 years old were not warfarin eligible for most of the trial.

\[ % \text{Ischemic Stroke or Systemic Embolism} \]

\[ \text{Warfarin (n=210)} \]
\[ \text{Placebo (n=211)} \]
\[ p = .01, \text{risk reduction 67\% (CI 27\% - 85\%)} \]

**Figure 2.** Plot of cumulative rate of primary events for warfarin versus placebo. CI, confidence intervals.
Similarly low rates of hemorrhage in patients assigned to warfarin have been reported in other recent clinical trials involving elderly atrial fibrillation patients\(^8,16\) and patients after myocardial infarction\(^7\).

The rate of primary events in patients assigned to placebo (6.3\% per year) was virtually identical to that prospectively predicted (6.0\% per year) from analysis of prior epidemiological and retrospective studies.\(^6,18\) To allow reliable central event verification, TIAs were not included as primary events even though many of these clinically transient events are associated with radiologic evidence of brain infarction. Considering ischemic stroke and TIA together, the risk of brain ischemia was 7.5\% per year in patients assigned to placebo. There may be subpopulations of atrial fibrillation patients with substantially lower risk who may not benefit from antithrombotic therapy, as suggested by retrospective studies of young patients with isolated "lone" atrial fibrillation not associated with other cardiopulmonary disease.\(^9\) Meta-analysis of the placebo arms of recent randomized trials may be necessary to convincingly define low-risk subgroups.\(^15,20-22\) Our results suggest that the majority of people more than 60 years old with atrial fibrillation would benefit from treatment with either aspirin or warfarin. Secondary analyses of constellations of relevant events (Figures 4 and 5) confirm the value of these antithrombotic agents in this population.

Three other clinical trials have also demonstrated that warfarin reduces the risk of stroke and systemic embolism in patients with nonrheumatic atrial fibrillation.\(^8,16,22\) The randomized Copenhagen AFASAK trial reported a minimal benefit of aspirin given in a dosage of 75 mg/day (risk reduction, 16\%).\(^8,23\) Details of compliance are not available for aspirin-assigned patients, mean patient age was 74 years, and, because of the small number of events, the 95\% confidence interval for the aspirin effect in AFASAK include the 42\% risk reduction found in SPAF. In the Copenhagen AFASAK trial, warfarin appeared superior to aspirin (risk reduction, 52\%; 95\% confidence interval, 2\%-77\%) by intention-to-treat analysis.\(^23\)

Pending demonstration of subpopulations with very low risk for stroke and embolism, antithrombotic therapy with aspirin or warfarin is indicated for most atrial fibrillation patients who can safely take these medications. The relative value of warfarin compared with aspirin is unclear, and the SPAF II Study is continuing to address this critical question in a larger number of patients during a longer period of observation.

### Appendix 1

SPAF Investigators Listed in Order of Number of Patients Enrolled

**Clinical Centers**

Hennepin County Medical Center and Abbott Northwestern Hospital, Minneapolis, Minn. David C. Ander-
FIGURE 3. Plot of cumulative rate of primary events for aspirin versus placebo. CI, confidence intervals.

TABLE 8. Major Complications*

<table>
<thead>
<tr>
<th>Allocation</th>
<th>Patients (n)</th>
<th>Observation period (patient-yr)</th>
<th>Intention to treat</th>
<th>Relevant bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>All</td>
<td>Rate (%/yr)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>210</td>
<td>260</td>
<td>4</td>
<td>1.5</td>
</tr>
<tr>
<td>Placebo</td>
<td>211</td>
<td>244</td>
<td>4</td>
<td>1.6</td>
</tr>
<tr>
<td>Aspirin</td>
<td>552</td>
<td>720</td>
<td>10</td>
<td>1.4</td>
</tr>
<tr>
<td>Placebo</td>
<td>568</td>
<td>731</td>
<td>14</td>
<td>1.9</td>
</tr>
</tbody>
</table>

*No other major complications were identified other than bleeding. See "Appendix 2" for specific criteria. Relevant bleeding was that which occurred within 14 days of receiving study drug and without a predictable precipitating cause for bleeding (e.g., major trauma, coronary bypass surgery). Sites of bleeding were 14 gastrointestinal, six central nervous system (CNS), and one each retroperitoneal, pericardial, joint, bronchial, and surgical. Sites of fatal bleeding were three CNS and two gastrointestinal. Residua includes fatal hemorrhages.

†CNS bleeding as follows: warfarin, one fatal intracerebral hemorrhage and one subdural hematoma with full recovery; aspirin, one fatal intracerebral hemorrhage and one fatal subdural hematoma; placebo, two subdural hematomas with full recovery.
FIGURE 4. Graph of risk reduction comparing warfarin with placebo. TIA, transient ischemic attack.

University of Miami School of Medicine, Miami, Fla. Roger E. Kelley, MD, Robert Chahine, MD, Lilian Cristo, RN, Maite Palermo, RN, BSN, Odalys Perez, RN, BSN, and Iliana Peña, MD.

The University of Arizona College of Medicine, Tuscon. William M. Feinberg, MD, Brenda K. Vold, RN, BSN, Karl B. Kern, MD, and Christopher Appleton, MD.

Northwestern University Medical School, Chicago. Vincent T. Miller, MD, Connie J. Hockersmith, RN, Bruce A. Cohen, MD, Gary J. Martin, MD, and Alan J. Pawlow, MD.

Mount Sinai Medical Center, New York. Jonathan L. Halperin, MD, Elizabeth B. Rothlauf, RN, Jesse M. Weinberger, MD, Martin E. Goldman, MD, Richard Goldman, MD, and Valentin Fuster, MD.

University of California-San Diego Medical Center. Howard C. Dittrich, MD, John F. Rothrock, MD, and Carol Hagenhoff, RN, MPH.

University of Illinois College of Medicine at Chicago and Peoria. Cathy M. Helgason, MD, George T. Kondos, MD, Julie Hoff, RN, MPH, Lisa Kaufmann, RN, BSN, R.R. Rabjohns, MD, R.P. McRae, MD, and J. Ghali, MD.

University of Iowa College of Medicine, Iowa City. Harold P. Adams Jr., MD, Ernest O. Theilen, MD, José Biller, MD, Donald D. Brown, MD, Ellis Eugene Marsh III, MD, Sara J. Sirna, MD, and Victoria L. Mitchell, RN.

University of Colorado School of Medicine, Denver, Colo. Robert M. Rothbart, MD, Gretchen H. Bailey, RN, and Carolyn Burkhardt, MD.

University of Texas at Houston. Gage van Horn, MD, Gerald V. Naccarelli, MD, and Deborah Grimm Wilson, RN.


Clinical Coordinating Center, University of Texas Health Science Center at San Antonio. Jonathan L. Halperin, MD, Robert G. Hart, MD, Carla P. Sherman, RN, BSN, David G. Sherman, MD, Robert L. Talbert, PharmD, Tina L. Dacy, and Elizabeth S. Schutz.

Safety Monitoring Committee. Theodore Colton, ScD, Boston University; David E. Levy, MD, Cornell University, New York; James D. Marsh, MD, Harvard University, Boston; and K.M.A. Welch, MD, Henry Ford Hospital, Detroit, Mich.

National Institute of Neurological Disorders and Stroke. John R. Marler, MD, Bethesda, and Michael D. Walker, MD, Bethesda, Md.

Writing committee for this report (in alphabetical order). Bruce A. Cohen, MD, Northwestern University, Chicago; George Feldman, MD, Kaiser Permanente, Portland, Ore.; Greg C. Flaker, MD, University of Missouri-Columbia; Robert G. Hart, MD, University of Texas, San Antonio; John H. McAnulty, MD, Oregon Health Sciences University, Portland; and Ruth McBride, Statistics and Epidemiology Research Corporation, Seattle, Wash.

Appendix 2

Diagnostic Criteria

Events*

"Ischemic stroke" was clinically defined as the abrupt onset over minutes to hours of focal neurological deficit in the distribution of a single brain artery persisting for more than 24 hours determined by the local SPAF-affiliated neurologist. Computed tomography was strongly encouraged to exclude primary hemorrhages; when computed tomography or autopsy data were not available to definitely exclude hemorrhage, such strokes were analyzed as primary events but classified as of uncertain cause. Focal deficits lasting less than 24 hours were classified as transient ischemic attacks (even if a new computed tomography lesion was present). Primary hemorrhages were classified separately as major complica-

*Criteria for secondary events are available on request.
tions; secondary hemorrhagic infarction was classified as an ischemic stroke.

Stroke severity was assessed at hospital discharge using a three tiered global scale: minimally disabling (no deficit or mild deficit but independent in basic activities of daily living), moderately or severely disabling (not independent and requiring assistance to perform basic activities of daily living), and fatal (death as a direct result of stroke within 30 days). In addition, the EC-IC post stroke functional disability scale was administered at discharge and 6 months after the stroke.

“Systemic embolism” was clinically defined as abrupt vascular insufficiency associated with clinical or radiologic evidence of arterial occlusion in the absence of other likely mechanisms (e.g., atherosclerosis, instrumentation). In the presence of atherosclerotic peripheral vascular disease, diagnosis of embolism to the lower extremities was made with caution and required arteriographic demonstration of abrupt arterial occlusion.

“Major complications” included any bleeding that involved the central nervous system, management requiring hospitalization with transfusion and/or surgery, or permanent residual impairment. All such bleeding episodes were recorded for the primary intention-to-treat analysis. However, a secondary efficacy analysis of “relevant bleeding” included only those occurring within 14 days of receiving study medication and not precipitated by circumstances independently associated with blood loss (e.g., transfusion at the time of coronary artery bypass surgery) to give a more clinically relevant estimate of the risk of major bleeding. In equivocal cases, hemorrhages were classified as “relevant bleeding.” Severe allergic reactions and warfarin-related skin necrosis were also classified as major complications.

“Deaths” were categorized as vascular (e.g., myocardial infarction, congestive heart failure, arrhythmia, stroke, pulmonary embolism), nonvascular (e.g., cancer, trauma, suicide, diabetic ketoacidosis, respiratory failure), probable vascular (e.g., sudden collapse with no other probable cause, un witnessed death with known history of coronary artery disease) or indeterminate by the Events Committee, the members of which were unaware of treatment allocation.

Other Diagnostic Criteria

“Hypertension” was defined as blood pressure exceeding 160 mm Hg systolic or 90 mm Hg diastolic on repeated observations over 3 months or as chronic antihypertensive therapy, if no pretreatment blood pressure values were available.

“Congestive heart failure” was classified as definite if currently present or on the basis of well-documented medical records if the patient had a constellation of orthopnea, dyspnea on exertion, or edema responding to diuretic therapy; S3 gallop and pulmonary rales; chest radiographic evidence of cardiomegaly or vascular redistribution; and elevated left ventricular filling pressure or pulmonary wedge pressure at catheterization. When medical records were incomplete or uncertain or coexistent pulmonary disease was confounding, a diagnosis of “possible-probable” congestive heart failure was assigned. Transient congestive heart failure associated with rapid ventricular response to atrial fibrillation was classified as definite if the above criteria were met.

“History of myocardial infarction” was defined as definite when any of the following were documented: serial electrocardiographic or enzyme changes compatible with myocardial infarction, history of compatible clinical syndrome of prolonged chest pain plus abnormal Q waves in appropriate electrocardiographic leads or diminishing R wave amplitude in two or more adjacent precordial leads and segmental left ventricular wall motion abnormality, and angiographic evidence of coronary occlusive disease with associated ventricular dysnergy. The presence of characteristic Q waves on electrocardiogram or segmental ventricular dysfunction without a clear clinical history was not considered definite prior myocardial infarction. History of probable myocardial infarction was used in less certain situations when less documentation was available: 1) hospitalization for acute chest pain, patient reports being told of a “heart attack,” no records available, and current electrocardiogram shows probable ischemic changes but no characteristic QRS changes; and 2) Q waves characteristic of remote myocardial infarction in a patient with angina but no clinical history of acute event (e.g., “silent” myocardial infarction).

“History of angina pectoris” required discomfort occurring anywhere in the anterior chest, back, jaw, neck, or shoulder requiring rest or nitroglycerin for relief; and/or medical record documenting history of angina by clinical symptoms and cardiac antianginal drug therapy; and/or history of an invasive cardiac procedure (i.e., percutaneous transluminal coronary angioplasty or coronary artery bypass graft surgery) for the treatment of anginal symptoms. “Definite” referred to a high degree of certainty that angina is present, often supported by resting or exercise electrocardiographic abnormalities, thallium imaging, and/or coronary angiograms. “Possible” described less certain situations.

“Pattern of atrial fibrillation” (constant versus intermittent) at the time of entry was based on the pattern of atrial fibrillation in the preceding 12 months. Atrial fibrillation was classified as constant if sustained for more than 3 weeks without intervening sinus rhythm. Intermittent atrial fibrillation required electrocardiographic evidence of sinus rhythm between episodes of atrial fibrillation within 12 months before entry.

References


KEY WORDS • thromboembolism • warfarin • aspirin • clinical trials • atrial fibrillation • cerebrovascular disorder
Stroke Prevention in Atrial Fibrillation Study. Final results.

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