Stroke Prevention in Nonvalvular Atrial Fibrillation

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There has been considerable uncertainty about the best way to prevent stroke in patients with nonvalvular atrial fibrillation. Recent studies have suggested that low-dose warfarin therapy, in addition to producing fewer bleeding complications, may be as effective as higher-dose therapy in preventing thromboembolic events. Four large, prospective, randomized trials have examined the risks and benefits of warfarin therapy for stroke prophylaxis in patients with nonvalvular atrial fibrillation. All four studies showed a substantially reduced incidence of stroke and a low incidence of significant bleeding in patients treated with warfarin. One of these studies also showed that aspirin reduced the incidence of stroke. The benefits associated with long-term low-dose warfarin therapy appear to exceed the risks for serious bleeding in most patients with atrial fibrillation. Aspirin may be a viable therapeutic option for patients who are unable to take warfarin or for those in subgroups at a low risk for stroke.


Dr. Gregory W. Albers (Department of Neurology and Neurological Sciences, Stanford University Medical Center, Stanford, California): Patients with atrial fibrillation have an increased risk for stroke. However, for most types of atrial fibrillation, the roles of both long-term anticoagulant therapy or long-term antiplatelet therapy for stroke prevention have been unclear. Until very recently, no prospective, randomized trials had evaluated treatment options for patients with atrial fibrillation. In the last few years, four large, prospective, randomized trials have examined the risks and benefits of antithrombotic therapy for stroke prevention in patients with atrial fibrillation (Table 1).

Because the study designs of these trials were similar, data on stroke occurrence and bleeding risk are now available from an exceptionally large group of patients with atrial fibrillation. Collectively, these studies represent over 4300 patient-years of follow-up in patients who were randomly assigned to warfarin, aspirin, or control groups. The purpose of our symposium was to review the evaluation and management of patients with atrial fibrillation, focusing on the effect of the recently available data on the roles of both low-dose anticoagulant therapy and antiplatelet therapy stroke prevention.

Cause, Evaluation, and Management of Atrial Fibrillation

Dr. J. Edwin Atwood (Division of Cardiology, Stanford University Medical Center, Stanford, California): Atrial fibrillation is a common arrhythmia, with a prevalence of approximately 2% in the general population (1). It is more common in the elderly, affecting about 5% of persons over 60 years of age (2, 3). The importance of atrial fibrillation is emphasized by its association with between 6% and 24% of ischemic strokes (4) and with about 50% of cardioembolic strokes (5).

The pathophysiology of atrial fibrillation is not fully understood. Several mechanisms have been suggested; these include fibrosis (particularly around the sinoatrial node), high atrial pressure, hypoxia and ischemia, atrial enlargement, and high autonomic tone (6, 7). The most commonly held hypothesis about the electrophysiology of atrial fibrillation is that proposed by Moe who suggested that atrial fibrillation is caused by multiple wavelets of re-entrant circuits with irregular contour (6). This may be due to high autonomic tone and a large atrium. However, rapid atrial pacing has also caused atrial fibrillation in both animals and humans, suggesting that automatic focus may be a mechanism. The successful response of patients with atrial fibrillation to direct-current cardioversion reinforces the theory that atrial fibrillation is a re-entrant arrhythmia.

Associated Disorders

Atrial fibrillation is usually associated with other conditions (Table 2). At one time, rheumatic valvular disease was the disorder most commonly associated with atrial fibrillation. Currently, nonvalvular heart disease accounts for more than 70% of the cases of atrial fibrillation (1). Coronary artery disease is present in about 50% of patients with atrial fibrillation; yet, atrial fibrillation occurs in only 1% to 2% of patients with coronary artery disease. Atrial fibrillation occurs as a complication of myocardial infarction in about 10% of cases (6). Because of its prevalence in the general population, hypertension is found in almost 60% of patients with atrial fibrillation; however, atrial fibrillation occurs in only 5% to 10% of hypertensive patients. Atrial fibrillation has been noted in as many as 10% of patients with...
with hypertrophic cardiomyopathy and in about 20% of patients with dilated cardiomyopathies (8, 9). Although atrial fibrillation may occur as a complication in 10% to 30% of patients with thyrotoxicosis, only about 2.5% of patients with atrial fibrillation have evidence of thyroid disease (10).

### Evaluation of Atrial Fibrillation

The diagnosis of atrial fibrillation is made using electrocardiography. In patients with atrial fibrillation, an electrocardiogram shows an absence of discrete atrial activity; an irregular undulating baseline; and a variable R-R interval. Determining the cause of atrial fibrillation usually requires a systematic evaluation. An examination of the heart using basic techniques is required, and new technology may sometimes be useful (Table 3) (11, 12).

### Therapy

Therapy for atrial fibrillation includes cardioversion, rate control, and long-term anticoagulation (which is discussed later).

#### Cardioversion

Two types of cardioversion are currently used: direct-current electrocardioversion and pharmacologic cardioversion. Several factors determine which patients are less likely to experience successful cardioversion and to maintain sinus rhythm. The likelihood of successful cardioversion or maintenance of sinus rhythm diminishes with increasing duration of atrial fibrillation, particularly if the duration is more than 1 year. Several investigators have suggested that a left atrial size of more than 45 mm indicates a poor likelihood of conversion to sinus rhythm, but recent data have shown successful cardioversion in patients with left atrial sizes of up to 60 mm (13, 14). Patients with digitalis intoxication and those in whom previous attempts at cardioversion have resulted in only transient successful maintenance of sinus rhythm are unfavorable candidates. Unlike patients with chronic atrial fibrillation, patients with acute atrial fibrillation of less than 3 days duration do not require anticoagulant therapy before cardioversion (15).

Direct-current cardioversion is initially successful in about 90% of patients. Pharmacologic cardioversion, using such drugs as quinidine, procainamide, disopyramide, flecainide, propafenone, and amiodarone, has been successful in as many as 80% of patients. Unfortunately, the proportion of patients who maintain sinus rhythm for 1 year, even with antiarrhythmic therapy, may be less than 50% (16). This success rate must also be balanced against the increased risk for sudden death that has been associated with some antiarrhythmic agents.

#### Rate Control

Digoxin, which is very effective in patients at rest, is the most commonly used agent for rate control. However, for patients in stress states (exercise, acute medical illness), catecholamines will override the atrioventricular nodal suppression induced by digoxin. Both β-adrenergic blockers and calcium-channel blockers (such as verapamil and diltiazem) have been effective in reducing heart rate response during exercise and the acute onset of atrial fibrillation (17, 18). Because of their negative inotropic effects, β-adrenergic blockers may cause reduced functional capacity (19).

### Low-Dose Oral Anticoagulants

Dr. Jack Hirsh (Department of Medicine, McMaster University, Hamilton, Ontario): Interest in the use of warfarin, a drug that has been in use for over 40 years, has been rekindled by the finding that low-dose warfarin therapy is effective for many indications and produces fewer bleeding complications when compared with the higher-dose therapy used in the past.

### Therapeutic Range for Oral Anticoagulant Therapy

Guidelines for monitoring oral anticoagulant therapy were reported recently (20, 21). An upper limit for the therapeutic range can be justified for most indications (20, 21); however, the lower limit has not been defined by clinical trials, and it is possible that the lower limit can be reduced even further for some indications.

Several different tests are used for the laboratory monitoring of anticoagulant therapy. The most com-

### Table 2. Diseases Associated with Atrial Fibrillation

<table>
<thead>
<tr>
<th>Disease</th>
<th>Prevalence in Patients with Atrial Fibrillation</th>
<th>Prevalence of Atrial Fibrillation in Each Disease</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valvular heart disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rheumatic valvular heart disease</td>
<td>20-30</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Nonvalvular heart disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>50-60</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>40-60</td>
<td>5-10</td>
<td></td>
</tr>
<tr>
<td>Pericarditis</td>
<td>&lt; 1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dilated</td>
<td>&lt; 1</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Hypertrophic</td>
<td>&lt; 1</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Alcohol (the holiday heart syndrome)</td>
<td>&lt; 1</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>After coronary bypass surgery</td>
<td>&lt; 5</td>
<td>30-40</td>
<td></td>
</tr>
<tr>
<td>Conductive system disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(the sick sinus syndrome, the Wolff-Parkinson-White syndrome)</td>
<td>&lt; 5</td>
<td>&lt; 5</td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>&lt; 1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Lone atrial fibrillation</td>
<td>10</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>2.5</td>
<td>20-30</td>
<td></td>
</tr>
</tbody>
</table>
monly used test is the one-stage prothrombin time (PT), which was introduced by Quick (22) in 1935. This test is sensitive to reductions in factors II, VII, and X. The interpretation of reported prothrombin times has been complicated by the fact that the thromboplastins in current use are prepared by different methods and vary in their responsiveness to reductions in vitamin-K-dependent clotting factors (20, 21, 23-25). This variability produces problems in anticoagulant control for patients who travel and has had important effects on the clinical management of patients in North America (25). When prothrombin-time testing was introduced in the 1940s, the thromboplastin reagents were prepared locally by hospital laboratories and were more responsive than the commercial thromboplastins currently used in North America but were of similar responsiveness to the thromboplastins currently used in the United Kingdom (25). Recommendations by the American Heart Association in 1948 that the therapeutic range for oral anticoagulant control should be equivalent to a prothrombin-time ratio of 2.0 to 2.5 were based on the use of responsive thromboplastins (26). The recommended range was not modified when the less responsive thromboplastins were introduced in the 1970s, leading to a systematic increase in the dose of warfarin used in North America. The recommended therapeutic range has now been adjusted downward for most indications.

Standardization of the Prothrombin Time

Over the years, several attempts have been made to standardize the reporting system for the prothrombin time (25, 27), and in 1983 the World Health Organization (WHO) introduced an acceptable reference preparation (24, 27) that allows the prothrombin-time ratio observed with a local thromboplastin to be converted into an international normalized ratio (INR). The INR is calculated as follows: INR = observed prothrombin-time ratio raised to the power C, where C represents the international sensitivity index (ISI). The ISI indicates the relation between the sensitivity of the local thromboplastin and the WHO reference thromboplastin. Thus, the INR is the prothrombin-time ratio that would have been obtained if the WHO reference thromboplastin had been used to conduct the test (24, 27). Some manufacturers of thromboplastins are now providing ISI values on request.

Dosing Considerations

The anticoagulant effect of warfarin is delayed until the normal clotting factors are cleared from the circulation (28). An anticoagulant effect occurs within 24 hours because of the suppression of factor VII activity, but peak anticoagulant activity is delayed for 72 to 96 hours because of the longer half-lives of factors II, IX, and X (29-32). Protein C has a short half-life (33), similar to that of factor VII (6 to 7 hours). Consequently, for the first 24 to 48 hours after the start of oral anticoagulant therapy, the reduction of factor VII activity may be counteracted by the thrombogenic effect of reduced protein C activity.

Two approaches to dosing can be used. If the need for antithrombotic therapy is not urgent (for example, in patients with chronic stable atrial fibrillation), warfarin therapy can be started using a daily average maintenance dose of 4 to 5 mg/d to achieve a steady-state anticoagulant effect in 4 to 6 days. If a more rapid anticoagulant effect is required, treatment with heparin and warfarin should be overlapped for 4 to 5 days; the daily dose of warfarin should be increased to 10 mg for the first 2 days, and heparin therapy should be discontinued after 4 to 5 days when the prothrombin time is in the therapeutic range. For most indications, a low-dose warfarin regimen is effective. The low-dose regimen refers to an INR of 2.0 to 3.0, which, when using a typical North American thromboplastin (ISI, 2.4), corresponds to a prothrombin-time ratio of 1.3 to 1.5.

Stroke Risk in Atrial Fibrillation

Dr. Albers: In general, the stroke rate for patients with chronic atrial fibrillation is about 5% per year (1, 5, 34). However, atrial fibrillation is a heterogeneous disorder, and, in certain subgroups, the stroke rate is higher than 5% per year, whereas other subgroups have a substantially lower rate of stroke.

Atrial fibrillation is associated with valvular and nonvalvular causes. In general, patients with valvular atrial fibrillation have a stroke rate of more than 5% per year when not receiving anticoagulant therapy, and long-term anticoagulation is well accepted as standard therapy (1, 35). Therefore, patients with most types of valvular atrial fibrillation were excluded from the randomized, prospective trials. Instead, the prospective trials focused primarily on nonvalvular atrial fibrillation, which is typically associated with hypertension or coronary artery disease. Certain subgroups of patients with nonvalvular atrial fibrillation have been identified as having a particularly high or low risk for stroke.

Patients with a High Risk for Stroke

Age is one of the primary determinants of the risk for stroke in patients with nonvalvular atrial fibrillation (36, 37). As patients age, the relative risk for stroke attributable to atrial fibrillation increases (36). In addition,
Table 4. Target Range for the Intensity of Anticoagulant Therapy and Aspirin Dose in the Prospective Studies of Atrial Fibrillation*

<table>
<thead>
<tr>
<th>Study</th>
<th>INR</th>
<th>PT ratio</th>
<th>Aspirin Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFASAK</td>
<td>2.8-4.2</td>
<td>1.5-2.0</td>
<td>75 mg/d</td>
</tr>
<tr>
<td>SPAF</td>
<td>2.0-3.5</td>
<td>1.3-1.8</td>
<td>325 mg/d</td>
</tr>
<tr>
<td>BAATAF</td>
<td>1.5-2.7</td>
<td>1.2-1.5</td>
<td>...</td>
</tr>
<tr>
<td>CAFA</td>
<td>2.0-3.0</td>
<td>1.3-1.6</td>
<td>...</td>
</tr>
</tbody>
</table>

* The relation between prothrombin-time ratios and international normalized ratios differ slightly among the studies because of the different sensitivities of local thromboplastins. INR = international normalized ratio; PT = prothrombin time; AFASAK = Copenhagen Atrial Fibrillation, Aspirin, Anticoagulation study; SPAF = Stroke Prevention in Atrial Fibrillation Study; BAATAF = Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA = Canadian Atrial Fibrillation Anticoagulation study.

Atrial fibrillation is a disorder of the elderly, with an average age of onset of about 65 years. Therefore, the treatment trials focused on elderly patients, and the average age in most trials was close to 70 years. In general, other subgroups of patients with nonvalvular atrial fibrillation who were at a high risk for stroke were excluded from the trials. These subgroups included patients with severe congestive heart failure, ventricular aneurysm, severe cardiomyopathy, documented intracardiac thrombus, or a recent embolic event.

Patients with a Low Risk for Stroke

Lone atrial fibrillation is typically defined as atrial fibrillation unaccompanied by clinical evidence of coexisting cardiovascular disease. Patients in this subgroup have been noted to have lower risk for stroke than do other patients with atrial fibrillation. Estimates of the risk for stroke have varied depending on the specific criteria used to define “lone” atrial fibrillation (38-41). Patients with lone atrial fibrillation who are less than 60 years of age appear to have a risk for stroke of less than 0.5% per year (4, 38). Because of this low risk, the Stroke Prevention in Atrial Fibrillation Study (SPAF) did not assign young patients with lone atrial fibrillation to warfarin therapy; instead, these patients were assigned to either aspirin or placebo.

The stroke risk associated with paroxysmal or intermittent atrial fibrillation has been controversial. Recent studies have suggested that the risk for stroke is lower in patients with paroxysmal fibrillation than in patients with chronic fibrillation (41, 42), although other studies have shown no significant difference (43). Patients with paroxysmal fibrillation were eligible in all trials (except the Copenhagen Atrial Fibrillation, Aspirin, Anticoagulation Study [AFASAK]) and composed about 15% of the total population studied.

Echocardiographic Factors

Echocardiographic factors associated with the risk for stroke in patients with atrial fibrillation have not been well defined. For example, no consistent relation between left atrial size and the risk for stroke has been documented in patients with nonvalvular atrial fibrillation (4, 41, 44-47). Transthoracic echocardiography has poor sensitivity for identifying left atrial or left atrial appendage thrombi. Transesophageal echocardiography is much more sensitive for identifying intracardiac thrombi in patients with atrial fibrillation and for documenting slow blood flow in the atrium, which may increase the risk for thromboembolism (48, 49). Transthoracic, but not transesophageal, echocardiography was done in all the prospective trials in an attempt to identify echocardiographic risk factors for embolization.

Risk Factors for Bleeding

Patients who were not good candidates for anticoagulant therapy were excluded from the prospective trials (except in the SPAF trial where such patients were randomly assigned to aspirin or placebo). Criteria for exclusion based on the risk for bleeding included bleeding disorders, previous hemorrhage, active peptic ulcer disease, alcoholism, uncontrolled hypertension, gait disorders, and severe renal or hepatic disease.

Another factor that affects bleeding risk is the intensity of anticoagulant therapy. Recommendations for the optimal intensity of oral anticoagulant therapy in the United States have been modified substantially over the last several years (20). The results of several clinical trials have suggested that low-intensity warfarin therapy (INR, 2.0 to 3.0; prothrombin-time ratio, 1.3 to 1.5) can provide equivalent protection against thromboembolic events as well as a substantially lower risk for bleeding in most situations (20).

The target range for the intensity of anticoagulant therapy varied to some extent in the prospective studies of atrial fibrillation. The intensity of therapy was highest in AFASAK (INR, 2.8 to 4.2; prothrombin-time ratio, 1.5 to 2.0) and lowest in the Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF) (INR, 1.5 to 2.7; prothrombin-time ratio, 1.2 to 1.5) (Table 4).

The Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation Study

Dr. Albers: The Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation Study (AFASAK) provided the first prospective, randomized evaluation of treatment options for patients with atrial fibrillation (50, 51). One thousand and seven patients with nonrheumatic atrial fibrillation were randomly assigned to treatment with aspirin, 75 mg/d, warfarin (INR, 2.8 to 4.2; prothrombin-time ratio, 1.5 to 2.0), or placebo. Aspirin and placebo were given in a double-blind fashion; the administration of warfarin was unblinded. A 2-year treatment duration was planned.

Risk factors for stroke, with the exception of age, were well distributed among the groups. Patients assigned to warfarin therapy were slightly younger (median age, 72.8 years) than patients assigned to aspirin (median age, 75.1 years) or placebo (median age, 74.6 years) (P < 0.03). This age difference could have provided a slight bias in favor of warfarin therapy because younger patients have a lower expected stroke rate.

An important problem in AFASAK was the large dropout rate in the warfarin group. Thirty-eight percent of the patients assigned to warfarin therapy withdrew...
before completion of the study, compared with only 13% and 15% in the aspirin and placebo groups, respectively. The most common reason for withdrawal from the warfarin group was the inconvenience of the frequent blood sampling. Patients receiving warfarin had an INR within the target range (2.8 to 4.2) for 42% of the treatment time. An INR of more than 4.2 occurred only 0.6% of the time, and an INR of less than 2.4 occurred 26% of the time.

Bleeding-related side effects occurred in 6% of patients assigned to warfarin therapy and in 1% of the patients assigned to aspirin therapy. No bleeding complications were reported in patients who received placebo. Only two of the bleeding episodes in patients who received warfarin were considered serious (one patient had a fatal intracerebral hemorrhage, and the other required a blood transfusion). One of the patients who was assigned to aspirin therapy also required a transfusion.

The trial was stopped prematurely by the data-monitoring statistician because of a substantial reduction in thromboembolic complications (stroke, systemic embolism, transient ischemic attack, or intracranial hemorrhage) in the warfarin group. Only 4 cerebral infarctions and 1 fatal intracerebral hemorrhage (INR, 3.7) occurred in the warfarin group, whereas 20 and 21 thromboembolic complications occurred in the aspirin and placebo groups, respectively. Of the four patients in the warfarin group who had cerebral infarctions, only one was receiving adequate anticoagulant therapy at the time of the event. Two patients had temporarily discontinued treatment, and one patient had a stroke on the day of randomization. Neither computed tomographic scans of the head nor autopsy results were available for 25% of the patients who had a stroke.

Despite the substantial dropout rate in the warfarin group, the intention-to-treat analysis also showed a reduction in total thromboembolic events (risk reduction, 56%; \( P = 0.056 \) (41)). The intention-to-treat analysis showed no significant reduction in thromboembolic events among patients receiving aspirin (21 events compared with 25 events in the placebo group).

A subgroup analysis showed that only patients with a history of previous myocardial infarction had an increased relative risk for stroke (52). Neither left atrial size nor duration of atrial fibrillation correlated with the risk for stroke.

In summary, the AFASAK trial provided the first substantial evidence that the benefits of anticoagulant therapy in patients with nonvalvular atrial fibrillation outweighed the risks associated with treatment. In addition, the study found no significant benefit associated with aspirin treatment (75 mg/d).

The Stroke Prevention in Atrial Fibrillation Study

Dr. David G. Sherman (Division of Neurology, University of Texas Health Science Center, San Antonio, Texas): The Stroke Prevention in Atrial Fibrillation Study (SPAF) was a multicenter study that compared both warfarin and aspirin therapy with placebo in patients with nonrheumatic atrial fibrillation (53). The study design called for the enrollment of 1644 patients over a 3-year period, with an additional year of follow-up before termination. However, the study was interrupted by the safety monitoring committee because a significant benefit was found to be associated with active therapy (either warfarin or aspirin) compared with placebo. When the study was stopped, 1330 patients had been randomized (mean follow-up, 1.3 years).

Enrollment criteria included electrocardiographic documentation of atrial fibrillation in the past year. Patients who required warfarin or aspirin therapy because of valvular heart disease or other cardiac or cerebrovascular indications were excluded from the study. Each eligible patient was evaluated to determine whether he or she was a candidate for anticoagulant therapy. Patients who were candidates for such therapy were randomly assigned equally to warfarin, aspirin, or placebo (group I). Warfarin was monitored in an open fashion (prothrombin-time ratio, 1.3 to 1.8; INR, 2.0 to 3.5). Enteric coated aspirin, 325 mg/d, was administered. Aspirin and placebo were administered in double-blind fashion. Patients who were not candidates for anticoagulant therapy or who refused to be considered for assignment to warfarin therapy were assigned to aspirin therapy or placebo (group II). Patients more than 75 years of age were excluded from group I during the initial phase of the study; however, this age restriction was subsequently eliminated. Patients less than 50 years of age who had lone atrial fibrillation were also excluded from group I. All patients had follow-up examinations every 3 months.

When the safety monitoring committee interrupted the study, 627 patients were enrolled in the anticoagulation group, and 703 were enrolled in the non-anticoagulation group. Their mean age was 67 years. Seventy one percent of these patients were men, 52% had a history of hypertension, and 34% had intermittent atrial fibrillation. Ten percent of these patients had definite angina pectoris, and 8% had had a previous myocardial infarction. Twenty-six percent of patients had a left atrial diameter of more than 5.0 cm, and 12% had moderate to severe ventricular dysfunction.

Data were analyzed on an intention-to-treat basis, and the primary end points were stroke and systemic embolism. Among patients in group I, those receiving warfarin therapy had 6 primary events (all strokes), whereas placebo recipients had 18 such events (17 strokes, 1 systemic embolism). These figures correspond to event rates of 7.4% per year in the placebo group and 2.3% per year in the warfarin group (risk reduction, 67%; 95% confidence interval (CI), 27% to 85%; \( P = 0.01 \)). Only two of the six patients receiving warfarin who had strokes were receiving adequate anticoagulant therapy; two patients had withdrawn from the study, and two had discontinued warfarin therapy 5 days previously and had normal prothrombin times.

Aspirin therapy was analyzed by combining data from group I and group II. The primary event rate in patients receiving aspirin was 3.6% per year compared with 6.3% per year in the placebo group (risk reduction, 42%; 95% CI, 9% to 63%; \( P = 0.02 \)). Of the 26 patients receiving aspirin who had primary events, 4 had not taken aspirin within 7 days of the event. Although an overall advantage of aspirin over placebo was found,
the benefit appeared to be greatest in younger patients. In fact, the event rate in patients who were more than 75 years of age was identical in both groups—7.4% per year.

Major bleeding, which was defined as hemorrhage severe enough to require hospitalization, blood transfusion, or surgery, occurred in 1.5% of patients receiving warfarin and included one intracerebral hemorrhage. The mean prothrombin-time ratio was 1.43, with a mean warfarin dose of 4.8 mg/d. The rate of major bleeding was 1.6% per year in placebo recipients and 1.4% per year in aspirin recipients. One aspirin recipient had an intracerebral hemorrhage.

The subgroup analysis did not indicate that left atrial size identifies patients at increased or diminished risk for stroke. However, patients with wall motion abnormalities identified by echocardiography did have an increased stroke rate.

A direct comparison of warfarin and aspirin was not done in this study because too few primary end-point events occurred in group I patients. This issue is being addressed by a new study, SPAF II, which includes patients from the original study who were either carried over or re-randomized.

In summary, the SPAF study found that the frequency of stroke is more than 5% per year in patients with atrial fibrillation. Both aspirin and warfarin are effective in reducing stroke in such patients, and this reduction can be accomplished with an acceptably low bleeding risk.

Boston Area Anticoagulation Trial for Atrial Fibrillation

Dr. Robert A. Hughes, on behalf of the BAATAF Investigators (Department of Cardiology, Harvard Medical School, Boston, Massachusetts): The Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF) was an unblinded, randomized, controlled study that was done to test the safety and efficacy of low-dose warfarin therapy for preventing stroke in patients with nonrheumatic atrial fibrillation (54). Patients were excluded if they required warfarin or aspirin therapy, or were at high risk for bleeding complications. Also excluded were patients at high risk for cardiogenic emboli (mitral stenosis, prosthetic valve, ventricular aneurysm, class IV heart failure, recent embolus).

Patients included in the study were randomly assigned to either treatment with warfarin (n = 212) or to a control group (n = 208). Because of the risks associated with anticoagulant therapy and the difficulty of maintaining blinding, neither treatment nor control was blinded. Accordingly, the control group did not receive placebo. The goal for the intensity of anticoagulant therapy was a prothrombin-time ratio of 1.2 to 1.5 (INR, 1.5 to 2.7). Control patients were allowed to take aspirin at the discretion of their personal physician. Aspirin treatment was nonrandomized; however, aspirin use was recorded for each patient.

The treatment and control groups were similar clinically. The average age of patients was 68 years, and 72% were male. Atrial fibrillation was intermittent in 17% of patients and had been present for less than 1 year in 32%. Approximately 15% of patients in both groups had diabetes, and about 25% had a history of congestive heart failure. About 50% had been smokers, and 51% in each group had hypertension.

The echocardiographic characteristics of both groups were also similar. The mean left atrial diameter was 41.9 mm in the warfarin group and 40.5 mm in the control group. Echocardiographic findings included substantial mitral regurgitation in about 25%, mitral annular calcification in about 30%, and ventricular dysfunction in approximately 25% of each group.

Two hundred and twelve patients received anticoagulant therapy for an average of 2.3 patient-years. Prothrombin times were checked every 2 to 3 weeks. Only 10% of the patients assigned to warfarin therapy permanently discontinued treatment with the drug. The mean prothrombin-time ratio was 1.33. Eighty-three percent of the prothrombin times were in the desired range; 9% were high, and 8% were low. The mean dose of warfarin was 4.2 mg/d.

The major outcome events included nonhemorrhagic stroke; major bleeding (defined as fatal or intracranial bleeding, or as bleeding that required transfusion with more than 4 units of blood in less than 48 hours); other systemic or extracranial embolus; and death. Data were subjected to an intention-to-treat analysis. Thirteen strokes occurred in the control group, whereas only 2 strokes occurred in the warfarin group; these data yield a stroke rate of 3.0% per patient-year in the control group and of 0.4% per patient-year in the treatment group (risk reduction, 86%; CI, 51% to 96%; P = 0.002). Only four of the strokes were classified as mild (good recovery); more than two thirds of the strokes resulted in substantial persistent neurologic deficits, and one patient had a fatal stroke. Neither of the strokes in the patients receiving warfarin was hemorrhagic. A secondary, nonrandomized analysis of patients who received aspirin showed that this treatment had no protective effect against stroke.

Subset analysis showed that the risk for stroke was influenced by three clinical variables in addition to treatment status. Patients who were more than 70 years of age or who had mitral annular calcification as shown by echocardiography had a fivefold increase in risk for stroke. Patients who had "lone atrial fibrillation" (no overt evidence of clinical heart disease) had one third the risk for stroke.

Mortality in the warfarin group (11 deaths) was also significantly less than that seen in the control group (26 deaths) (risk reduction, 62%; CI, 17% to 82%; P = 0.005). This reduction in death rate was present for both cardiac and noncardiac deaths.

Forty-six percent of control patients took aspirin regularly, usually 325 mg daily. The subset analysis failed to show any evidence of stroke reduction in control patients who took aspirin compared with control patients who did not take aspirin.

The incidence of hemorrhage in patients receiving warfarin was extremely low. Major hemorrhage occurred only twice in 487 patient-years of warfarin therapy, for a rate of 0.4% per patient year; one patient had a nonfatal gastrointestinal hemorrhage, and the other patient developed progressive obtundation and died af-
ter a fall (presumed intracranial hemorrhage). One non-fatal hemorrhage occurred in the control group.

The incidence of minor hemorrhage was higher in the treatment group than in the control group. Minor bleeding occurred in 38 patients receiving warfarin (7.8% per year) and in 21 controls (4.8% per year). Only 4 of the 38 warfarin recipients with bleeding were hospitalized, and only 2 required transfusion.

The Boston Study demonstrated that low-intensity anticoagulant therapy in patients with nonrheumatic atrial fibrillation is achievable and safe. In addition, the benefit in stroke reduction was 86%. We believe that, in general, this benefit outweighs the risk for major hemorrhage.

The Canadian Atrial Fibrillation Anticoagulation Study

Dr. Stuart J. Connolly, on behalf of the CAFA study Investigators (Faculty of Health Science, McMaster University, Hamilton, Ontario): The Canadian Atrial Fibrillation Anticoagulation (CAFA) study (55) was a randomized, double-blind, multicentered, placebo-controlled trial of warfarin in patients with nonrheumatic atrial fibrillation. Patients were eligible if they had either chronic or paroxysmal atrial fibrillation without mitral stenosis. Patients were excluded from the study if they either required or had a contraindication to anticoagulant therapy.

The study was designed to enroll 630 patients over 4 years, with a common termination of follow-up at the end of the fifth year. However, because of the positive results reported by the Copenhagen AFASAK study and the SPAF study, the CAFA study was terminated after recruiting only 383 patients. Of the 383 patients who were randomly assigned to a group, five were judged to be ineligible, leaving 187 patients in the warfarin group and 191 in the placebo group. The mean duration of follow-up was 15.2 months. The mean age was 68.0 years in the warfarin group and 67.4 years in the placebo group. About 75% of patients were male. Paroxysmal atrial fibrillation was present in 6.4% of warfarin recipients and in 7.3% of placebo recipients. Atrial fibrillation lasted less than 1 year in 19.8% of patients receiving warfarin and in 18.3% of patients receiving placebo. In both groups, the mean left atrial size was 46 mm, and the mean left ventricular end-diastolic size was 52 mm. Twenty-six percent of patients receiving warfarin and 23% of the placebo patients stopped taking their study medication at an early stage of the study. The target range for anticoagulation intensity was an INR of 2.0 to 3.0. Values above 3.0 occurred 17% of the time, and values below 2.0 occurred 39.6% of the time. Unblinding occurred in only 17 patients.

The primary outcome variables in this study were nonlacunar stroke, non-central nervous system embolism, intracranial hemorrhage, and other fatal hemorrhage. The primary analysis was based on the efficacy principle: Events were included in the analysis if they occurred before or within 28 days of permanent discontinuation of study medication. Eleven primary outcome events occurred in the placebo group and 7 occurred in the warfarin group, yielding annual event rates of 3.5% for warfarin and 5.2% for placebo. The relative risk reduction was 37% (95% CI, -63.5 to 75.5; P = 0.17). In an intention-to-treat analysis, the rates of primary outcome events were 3.4% per year in patients receiving warfarin and 4.6% per year in patients receiving placebo (relative risk reduction, 26%; 95% CI, -83.0% to 70.4%, P > 0.2).

Two of the primary events in the study were fatal hemorrhages, and both occurred in patients receiving warfarin therapy. When these hemorrhages are excluded from the primary analysis and the efficacy principle is used, the annual combined event rate for nonlacunar stroke and non-central nervous system embolism is 2.5% in the warfarin group and 5.2% in the placebo group (risk reduction, 55%; 95% CI, 30.4% to 84.3%; P = 0.07).

Six patients in the warfarin group had nonhemorrhagic primary outcome events: Five patients had cere-

### Table 5. Efficacy of Warfarin for the Prevention of Stroke*

<table>
<thead>
<tr>
<th>Variable</th>
<th>AFASAK</th>
<th>SPAF†</th>
<th>BAATAF</th>
<th>CAFA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Person-years of follow-up</td>
<td>413</td>
<td>244</td>
<td>435</td>
<td>250</td>
</tr>
<tr>
<td>Strokes, n</td>
<td>19</td>
<td>17</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>Stroke events/100 per year</td>
<td>4.6</td>
<td>7.0</td>
<td>3.0</td>
<td>3.6</td>
</tr>
<tr>
<td><strong>Warfarin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Person-years of follow-up</td>
<td>412</td>
<td>260</td>
<td>487</td>
<td>240</td>
</tr>
<tr>
<td>Strokes, n</td>
<td>8</td>
<td>6</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Stroke events/100 person-years</td>
<td>1.9</td>
<td>2.3</td>
<td>0.4</td>
<td>2.1</td>
</tr>
<tr>
<td>Risk reduction (95% CI), %</td>
<td>58 (7 to 81)</td>
<td>67 (1 to 86)</td>
<td>86 (51 to 96)</td>
<td>42 (68 to 80)</td>
</tr>
<tr>
<td>P value†</td>
<td>0.03</td>
<td>0.01</td>
<td>0.002</td>
<td>&gt; 0.2</td>
</tr>
</tbody>
</table>

*Intention-to-treat analysis. Strokes represent all strokes, regardless of suspected cause. Transient ischemic attacks, systemic emboli, and intracranial hemorrhages are not included. AFASAK = Copenhagen Atrial Fibrillation, Aspirin, Anticoagulation study; SPAF = Stroke Prevention in Atrial Fibrillation study; BAATAF = Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA = Canadian Atrial Fibrillation Anticoagulation study.
† Data are from group I only (see text).
‡ Controls received placebo in all studies except BAATAF; in BAATAF, 46% of the control patients took aspirin and 54% received "no treatment."
§ By chi-square analysis.
randomized studies of atrial fibrillation. The positive results for warfarin found in the three other studies is therefore consistent with and supportive of this study is therefore consistent with and supportive of the positive results for warfarin found in the three other randomized studies of atrial fibrillation.

Major bleeding was defined as a hemorrhage that resulted in a decrease in hemoglobin of at least 20 g/L, or as bleeding that required either a blood transfusion of at least two units or surgical treatment. While patients were taking study medication, five major hemorrhages occurred in the warfarin group (2.5% per year), and one major hemorrhage occurred in the placebo group (0.5% per year). One additional major hemorrhage occurred in a placebo recipient after the discontinuation of therapy. Bleeding of any type occurred in 16% of patients receiving warfarin and in 9% of patients receiving placebo.

Four of the nine strokes in the placebo group and two of the five strokes in the warfarin group were judged to be severe. The secondary outcome events were transient ischemic attack, lacunar infarction, death, and vascular death. The groups did not differ significantly regarding the frequency of any of these events.

Although the reduction in the risk for systemic embolism that was attributable to warfarin therapy in this study was not statistically significant, the study lacked statistical power. The study was designed to detect a 50% reduction in the risk for primary outcome events, with an enrollment of 630 patients who were to have a mean follow-up of 2.5 years; however, only about a third of the total expected patient-years of follow-up were obtained. The trend in favor of warfarin seen in this study is therefore consistent with and supportive of the positive results for warfarin found in the three other randomized studies of atrial fibrillation.

**Summation**

Dr. Albers: The prospective trials have confirmed that the rate of stroke in patients with nonvalvular atrial fibrillation is substantial—about 5% per year. More important, they have convincingly documented that low-dose warfarin therapy can substantially reduce stroke (Table 5 and Figure 1) with a minimal risk for significant hemorrhage in properly chosen patients with nonvalvular atrial fibrillation (Table 6).

These well-designed studies represent a major achievement. It is striking that four independent groups addressing the same issue all obtained such similar results. The reduction in the risk for stroke that was attributable to warfarin was substantial in all four studies and the yearly rate of major bleeding or intracerebral hemorrhage varied only minimally among studies (see Table 6).

The highest estimate of the reduction in the stroke rate as a result of warfarin therapy (86%) was obtained in the BAATAF study. This study had a low dropout rate (10%) and reported the highest degree of compliance with therapy (83% of prothrombin times were within the desired range). In the other three studies, more than 75% of the strokes experienced by patients randomized to warfarin therapy occurred at times when patients had either discontinued therapy or had prothrombin times that were substantially below the desired range. The desired therapeutic range for anticoagulation varied from an INR of 1.5 to 2.7 in the BAATAF trial to 2.8 to 4.2 in the AFASAK study. No evidence was found that higher intensities of anticoagulant therapy are more effective than lower intensities.

Before these studies, most physicians did not elect to administer anticoagulant therapy to patients with nonvalvular atrial fibrillation, primarily because of concern...
Table 7. Efficacy of Aspirin for the Prevention of Stroke\(^*\)

<table>
<thead>
<tr>
<th>Variable</th>
<th>AFASAK</th>
<th>SPAF(^f)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Person-years</td>
<td>413</td>
<td>731</td>
</tr>
<tr>
<td>Strokes, (n)</td>
<td>19</td>
<td>42</td>
</tr>
<tr>
<td>Stroke events/100 person-years</td>
<td>4.6</td>
<td>5.8</td>
</tr>
<tr>
<td>Aspirin(^t)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Person-years</td>
<td>413</td>
<td>720</td>
</tr>
<tr>
<td>Strokes, (n)</td>
<td>16</td>
<td>23</td>
</tr>
<tr>
<td>Stroke events/100 person-years</td>
<td>3.9</td>
<td>3.2</td>
</tr>
<tr>
<td>Risk reduction (95% CI)</td>
<td>16 (61 to 56)</td>
<td>44 (9 to 66)</td>
</tr>
<tr>
<td>(P) value</td>
<td>&gt;0.5</td>
<td>0.02</td>
</tr>
</tbody>
</table>

* All data represent the intention-to-treat analysis. Strokes represent all strokes regardless of suspected cause. Transient ischemic attacks, systemic emboli, and intracranial hemorrhages are not included.

\(^t\) SPAF data are from group I and group II combined (see text).

\(^t\) Aspirin dose was 75 mg/d in AFASAK and 325 mg/d in SPAF.

\(^\dagger\) By chi-square analysis.

that the risk for bleeding would outweigh the benefit. Undoubtedly, the results of these studies will alter this perception, for it now appears that most patients with nonvalvular atrial fibrillation are who are candidates for anticoagulation will benefit from chronic warfarin therapy.

Despite this important finding, several important questions remain unanswered. The stroke rate in young patients with atrial fibrillation who did not have other cardiovascular disease is known to be very low (less than 0.5% per year). The amount of stroke reduction these patients could expect from anticoagulant therapy is limited and probably would be negated by the risk for bleeding. However, as these patients become older, their risk for stroke increases and eventually may reach a point where benefit from anticoagulant therapy could be expected. How such a point is determined in an individual patient has not been answered.

The optimal management of other subgroups that were not well represented in the populations studied, such as patients with paroxysmal atrial fibrillation, also continues to be unclear. Also unresolved is how long warfarin therapy should be continued; the average duration of follow-up in these trials was less than 2 years. It is possible that as patients age, their risk for bleeding increases, thereby decreasing the net benefit of anticoagulant therapy. A meta-analysis of the data from these studies has been planned and will attempt to clarify some of these issues.

The role of aspirin for the prevention of stroke in patients with atrial fibrillation is also less clear. Only two studies randomly assigned patients to aspirin treatment (Table 7). The SPAF study was able to document a substantial reduction in the stroke rate in patients receiving aspirin, 325 mg/d, particularly in younger patients. The AFASAK trial was unable to document a substantial benefit in patients receiving a 75-mg daily dose of aspirin; however, this study enrolled fewer patients, and the confidence intervals were wide. Further investigation of the role of aspirin for stroke prevention in patients with atrial fibrillation is in progress. Until additional data are available, it appears reasonable to consider aspirin therapy for young patients with lone atrial fibrillation and for patients who are poor candidates for anticoagulant therapy.

An important disadvantage of chronic anticoagulant therapy is the requirement that the intensity of therapy be monitored frequently. Future options include evaluation of therapy with even lower doses of warfarin or of therapy combining very low doses of warfarin with aspirin. Such therapies may provide protection from thromboembolic events as well as the additional advantage of reduced monitoring.

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References


