Preventing Stroke in Patients With Atrial Fibrillation

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Atrial fibrillation has been variously described as rebellious palpitations, delirium cordis, and pulsus irregularis perpetuus by physicians since early times. In 1906, Einthoven reported the first electrocardiographic demonstration of atrial fibrillation. Later, Lewis and Rothberger and Winterberg confirmed the relationship between electrocardiographically documented atrial fibrillation and the clinical disorder of a chronic irregularly irregular pulse.

The prevalence of atrial fibrillation in developed countries increases rapidly with age. In patients aged 50 to 59 years, it occurs in only 0.5% of the population. Between 60 and 69 years, the prevalence is about 3.8% for men and slightly less for women; in those older than 70 years, the estimated prevalence is 9%. In a community-based Minnesota study, 16.1% of men and 12.2% of women older than 75 years had atrial fibrillation. A British study of patients seen in a general practice setting confirms these findings.

In developing countries, rheumatic heart disease accounts for most cases of atrial fibrillation, and the predominant incidence is in the young. In Western societies, however, when atrial fibrillation occurs in the young it is usually an isolated phenomenon, without predisposing structural heart disease, hypertension, or diabetes. These patients, usually younger than 60 years, have what is termed lone atrial fibrillation and are at low risk for systemic embolism. Although mainly an acquired disease, rare familial cases of atrial fibrillation are associated with a locus on chromosome 10, segregating with high penetrance, in an autosomal dominant pattern. These patients might provide clues to the pathogenesis of atrial fibrillation, which could lead to better treatment options.

Atrial fibrillation is a significant marker for both a higher incidence of stroke and increased mortality. In the Framingham Cohort Study, the risk of stroke was 5.6 times greater in patients with atrial fibrillation than that in comparably aged patients in sinus rhythm. In patients who also have rheumatic mitral stenosis, the risk of stroke is 17 times higher. The risk of developing a stroke varies with age. The cumulative incidence of stroke among patients 60 years or younger with lone atrial fibrillation is not significantly different from that in a control population matched for age and sex: 0.5%/y. In the elderly group, however, the risk is much higher, often exceeding 10%/y. Thus, determining the protection afforded by warfarin is most pronounced in patients at the highest risk for stroke, while aspirin treatment seems adequate in low-risk populations.
which patients are at highest risk and the most effective treatment for at-risk patients are important clinical issues.

**METHODS**

**Data Sources**

We used the MEDLINE database to search for completed, prospective, randomized trials published between January 1, 1966, and February 23, 1999, of stroke prevention in atrial fibrillation that evaluated either warfarin or aspirin therapy alone or in combination. Search terms were atrial fibrillation, stroke, warfarin, aspirin, aspirin and warfarin, randomized controlled trials, cerebral infarction, prevalence, dementia, and echocardiography.

**Study Selection**

Four types of clinical trials were found. Five placebo-controlled trials addressed primary prevention.16-20 One trial addressed secondary prevention in patients who had a stroke while in atrial fibrillation.21 The Stroke Prevention in Atrial Fibrillation II (SPAF II)22 study compared warfarin with aspirin therapy, and SPAF III23 evaluated warfarin and aspirin in combination. Two other studies evaluated fixed, minidose warfarin in combination with aspirin, both against international normalized ratio (INR)-adjusted-dose warfarin. These 2 studies were terminated early due to the results of SPAF III and were not included in our analysis.24,25

**Data Extraction**

Data from the primary prevention trials had previously been pooled,26 and the pooled data are presented. The secondary prevention, warfarin-aspirin comparison, and warfarin-aspirin combination trials are presented as single studies. Information has also been included on echocardiography27-32 and silent cerebral ischemia.33-36

**RESULTS**

**Primary Prevention**

The 5 primary prevention studies were independently designed and include the Atrial Fibrillation, Aspirin, Anticoagulation Study from Copenhagen, Denmark (AFASAK),10 the Stroke Prevention in Atrial Fibrillation (SPAF I) study,17 the Boston Area Anticoagulation Trial in Atrial Fibrillation (BAATAF),18 the Canadian Atrial Fibrillation Anticoagulation (CAFA) study,19 and the Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation (SPINAF) study.20 Patients requiring anticoagulation for other reasons or having contraindications to warfarin or aspirin were excluded.16-20 The average length of follow-up ranged between 1.2 and 2.3 years.37 All trials, except the Canadian trial, were terminated early because of the benefit demonstrated with warfarin. The Canadian trial was terminated because of the definitive results of the other studies.

In a formal pooled analysis of these trials, conducted collaboratively by the principal investigators of each of the trials, the value of warfarin was consistent among trials and, in aggregate, decreased the risk of stroke by 68% (4.5% to 1.4%/y) with virtually no increase in the frequency of major bleeding (the rates were 1.2%, 1.0%, and 1.0%/y for warfarin, aspirin, and placebo groups, respectively) (FIGURE). It was further determined that increasing age and a history of hypertension, diabetes, previous transient ischemic attack, or heart failure; arterisk, data from the Atrial Fibrillation Investigators; dagger, data from the Stroke Prevention in Atrial Fibrillation Investigators; double dagger, data from the European Atrial Fibrillation Trial Study Group; and section mark, data from the Stroke Prevention in Atrial Fibrillation III (SPAF III).23 The SPAF III study evaluated warfarin and aspirin in combination. The dose of warfarin in the combination arm was low and thus that arm of the study most likely represents an effect due to aspirin alone.

![Figure](image.jpg)

**Figure.** Expected Stroke Rates With Placebo, Warfarin, and Aspirin in Patients With Atrial Fibrillation

A minus sign indicates no risk factors; plus sign, at least 1 risk factor (history of hypertension, history of diabetes, previous transient ischemic attack, or heart failure); asterisk, data from the Atrial Fibrillation Investigators; double dagger, data from the European Atrial Fibrillation Trial Study Group; and section mark, data from the Stroke Prevention in Atrial Fibrillation III (SPAF III).23 The SPAF III study evaluated warfarin and aspirin in combination. The dose of warfarin in the combination arm was low and thus that arm of the study most likely represents an effect due to aspirin alone.

Younger than 65 years without these risk factors, even without anticoagulation, the stroke risk was 1%/y. These patients would not benefit from warfarin therapy. All other warfarin-eligible patients would benefit from warfarin treatment (event rate reduction from 3.5%-8.1%/y to 1.1%-1.7%/y). The SPAF III study, discussed later, identified a low-risk group, aged 65 to 75 years, who would benefit from aspirin therapy and had an event rate of 1.4%/y.26 The overall effect of warfarin was particularly beneficial in women, with an 84% reduction in stroke rate (for men, the reduction was 60%).

Aspirin was evaluated in 2 of these studies but in different doses: 75 mg/d for the AFASAK study10 and 325 mg/d for SPAF 1.17 In the BAATAF study,18 patients in the control group were allowed to take 325 mg/d of aspirin. Both the CAFA19 and the SPINAF20 studies excluded patients who used aspirin or nonsteroidal anti-inflammatory drugs.

In the AFASAK study, the incidence of thromboembolic complications and vascular mortality among patients taking aspirin was not significantly different from the incidence of these complications in the placebo group. In the SPAF 1 trial, aspirin use was associated with a 42% reduction in stroke. In the BAATAF study, patients in the control group were allowed to use
aspirin, but no benefit was seen. Overall, the reduction of stroke afforded by aspirin compared with placebo was 36%. Hence, the primary prevention trials proved warfarin’s superiority over both aspirin and placebo. In addition, it is generally agreed, although controversial, that aspirin is more effective in preventing stroke than placebo. Additionally, there is a lack of consensus regarding the optimal dose of aspirin, although 325 mg/d has been tested most extensively.

**Echocardiography for Risk Stratification**

**Transthoracic Echocardiography.** Three of the primary prevention studies, SPAF-I,17 BAATAF,18 and SPINAF,20 collected echocardiographic data at baseline, affording a unique opportunity to determine echocardiographic predictors of an increased risk of stroke, independent of the clinical predictors described above. The Atrial Fibrillation Investigators pooled the data from 1041 patients.27 Intraventricular septal thickness (mean [SD], 11.6 [3] mm vs 11 [2] mm; P = .02) and moderate to severe reduction in left ventricular function were univariate predictors of an increased risk of stroke. The only independent predictor of an increased risk of stroke identified from echocardiography was moderate to severe left ventricular dysfunction (relative risk [RR], 2.89; 95% confidence interval [CI], 1.67-5.01; P < .001). Left atrial size, even adjusting for body surface area, was not found to be an independent predictor of stroke risk.

Thus, moderate to severe left ventricular dysfunction is an independent risk factor for stroke in patients with atrial fibrillation, and these patients should be strongly considered for anticoagulant therapy. This information is most useful in those patients who do not have other clinical risk factors and in whom the risk without the transthoracic echocardiography would have been considered low.

**Transesophageal Echocardiography.** The role of transesophageal echocardiography (TEE) in stratifying the risk of embolization in atrial fibrillation has not been established, despite it being the most sensitive clinical tool available for detecting left atrial thrombus and spontaneous echo contrast. Both of these conditions are a consequence of reduced atrial flow velocities and left atrial contraction dysfunction caused by atrial fibrillation. The appearance of spontaneous echo contrast, a swirling mass of fine echoes, also described as echo “smoke,” on the TEE image of the left atrium indicates blood stasis and the presence of thrombus and is a marker for increased risk of thromboembolism.28,29 These conditions are not easily imaged by transthoracic echocardiography because the surface echocardiogram has a limited view of the left atrial appendage—the site at which most atrial thrombi form in patients with atrial fibrillation.29 While it is possible to identify patients at high risk for embolism, TEE has not been proved to provide incremental information to guide decision making regarding anticoagulation. Furthermore, the absence of left atrial thrombus or spontaneous echo contrast does not necessarily infer a low risk.

**Transesophageal echocardiography** may be indicated for patients requiring cardioversion. Manning et al29 have advocated the initial use of TEE to screen for thrombi. Cardioversion can then be performed in patients without thrombi with limited risk of stroke while anticoagulated with heparin.30 This approach theoretically would lead to better long-term results because the precardioversion duration of atrial fibrillation, which is inversely proportional to atrial recovery following cardioversion, would be shortened.32 Therapeutic heparin or warfarin at the time of cardioversion should be used and warfarin should be continued for at least 1 month following cardioversion. Continued anticoagulation is advised since cardioversion produces stunning of the atrium with loss of mechanical function and therefore a predisposition to clot formation and embolization.30

In our opinion, TEE-guided cardioversion may be particularly helpful in hospitalized patients, preventing a second admission. Stable outpatients can also be treated with 3 to 4 weeks of anticoagulation prior to cardioversion, unless it is shown that early cardioversion results in better long-term maintenance of sinus rhythm.

**Secondary Prevention**

The only published secondary prevention trial identified by our search is the European Atrial Fibrillation Trial.21 The cohort consisted of 1007 patients from 108 centers with nonrheumatic atrial fibrillation with a recent TIA or minor ischemic stroke. A total of 669 patients (warfarin-eligible group 1) were randomized to either open anticoagulation or further randomized to double-blind treatment with either 300 mg/d of aspirin or placebo. The 338 patients with contraindications to anticoagulation (group 2) were randomized to receive only aspirin or placebo. The main outcome measures were death due to vascular disease, any stroke, myocardial infarction, or systemic embolism. Patients with chronic and poorly controlled hypertension, history of hemorrhagic cerebral infarction, retinopathy, chronic alcoholism, noncompliance, or refusal to use anticoagulants were not included in the study.

During a mean follow-up of 2.3 years, the annual rate of outcome events was 8%/y in patients in the anticoagulant group and 17%/y in the placebo group (in group 1). Warfarin use reduced the risk of stroke from 12%/y to 4%/y (66% reduction). Among all patients assigned to aspirin, the incidence of outcome events was 15%/y compared with 19%/y among the patients receiving placebo (in group 2). The incidence of major bleeding complications was low in this study: 2.8%/y in the anticoagulant group, 0.9%/y in the aspirin group, and 0.7%/y in the placebo group. Fatal intracerebral hemorrhage occurred in 3 patients: 1 in the placebo and 2 in the aspirin group.

This study shows that in patients with nonrheumatic atrial fibrillation and recent TIA or minor stroke, anticoagu-
lant treatment reduces the risk of recurrent stroke by two thirds. The incidence of recurrent stroke was 12%/y in the placebo group, almost 3 times as high as in the placebo group of the primary prevention trials. Given the high efficacy of anticoagulation, treatment should be started as soon as possible. Some have recommended withholding anticoagulants during the first few days after suspected stroke, especially if the infarct is large, to prevent hemorrhagic transformation.

**Warfarin vs Aspirin: Direct Comparison**

The SPAF II study consisted of 2 parallel clinical trials involving 1100 patients entered between 1987 and 1992 at 16 clinical centers. Data were analyzed separately according to age: 75 years or younger or older than 75 years at the time of enrollment. This study excluded patients with lone atrial fibrillation. The aim of SPAF II was to determine whether warfarin administered at a prothrombin time of 1.3 to 1.8 seconds and an INR of 2.0 to 4.5 would reduce the risk of primary events compared with aspirin, 325 mg/d. The primary event rate was 1.3%/y with warfarin and 1.9%/y with aspirin (RR, 0.67; P = .24), and by an intention-to-treat analysis there was no benefit from warfarin. It is important to note, however, that the stroke rate was low in this study, reducing its power to show a difference between 2 effective treatments.

Patients older than 75 years were found to have a substantial risk of thromboembolism during aspirin therapy (4.8%/y). Warfarin reduced the risk to 3.6%/y (RR, 0.73; P = .39). Many elderly patients, however, were unable to sustain long-term anticoagulation, and the risk of bleeding, particularly intracranial hemorrhage, was increased during anticoagulation. The higher intracranial hemorrhage rate of 1.8%/y compared with the 0.3%/y rate in the primary prevention studies is attributable to higher levels of anticoagulation. It is generally believed that increasing age may also constitute a risk factor for intracerebral hemorrhage, as documented with thrombolytic therapy.

This trial highlighted that anticoagulation therapy in the elderly should be kept in a narrow range, probably not exceeding an INR of 3.0. In addition, it is prudent to maintain blood pressure well within the normal range.

**Warfarin and Aspirin in Combination**

The SPAF III study evaluated 1044 patients with atrial fibrillation who also had at least 1 prespecified risk factor for thromboembolic disease, including congestive heart failure or left ventricular fractional shortening of less than 25%, previous thromboembolism, systolic blood pressure higher than 160 mm Hg, or being a woman older than 75 years. Patients were randomly assigned to either a combination of low-intensity fixed-dose warfarin, adjusted to an INR of 1.2 to 1.5 for initial dose adjustment, and aspirin 325 mg/d, or to adjusted-dose warfarin for an INR of 2.0 to 3.0. The mean INR in the combination group was 1.3 compared with 2.4 for those taking adjusted-dose warfarin. The trial was terminated after a mean follow-up of 1.1 years when the rate of ischemic stroke and systemic embolization in the combination therapy group was 7.9%/y compared with 1.9%/y in the dose-adjusted group (P = .001). The rates of major bleeding were similar in both treatment groups. Thus, following the regimen of low-intensity fixed-dose warfarin plus aspirin was not sufficient for stroke prevention in patients with nonvalvular atrial fibrillation who were considered at high risk for thromboembolic complications. This study further confirmed the benefit of therapeutic doses of warfarin over aspirin; the subtherapeutic dose of warfarin in the combination arm did not confer a benefit.

**Ideal Therapeutic Range for Anticoagulation**

From the results of several studies, it appears that anticoagulation therapy with warfarin should be monitored carefully. An INR of between 2.0 and 3.5 is the optimum range for most indications. Among elderly patients, however, an upper limit to the INR of approximately 3.0 is appropriate.

**Silent Cerebral Infarction**

Cerebral infarction in patients with atrial fibrillation may vary from being clinically silent to catastrophic. The prevalence of silent cerebral infarction and its effect as a risk factor for symptomatic stroke are important considerations for the evaluation of patients with atrial fibrillation.

The Veterans Affairs Cooperative Study was a double-blind controlled trial designed primarily to determine the efficacy of warfarin for the prevention of stroke in neurologically normal patients with nonrheumatic atrial fibrillation. It also was designed to evaluate patients with silent cerebral infarction. Computed tomography of the head was performed at entry, at the time of any subsequent stroke, and at termination of follow-up.
on all patients who completed the study without a neurological event. Of 516 evaluable scans obtained at entry, 76 (14.7%) had evidence of 1 or more silent infarcts. Age (P = .01), a history of hypertension (P = .003), active angina (P = .01), and elevated mean systolic blood pressure (P < .001) were associated with silent infarcts. Silent cerebral infarction occurred during the study at rates of 1.01%/y and 1.57%/y for the placebo and warfarin treatment groups, respectively (RR, 1.55; 95% CI, 0.40-6.11). Silent cerebral infarction at entry was not an independent predictor of later symptomatic stroke, but active angina was a significant predictor: 15% of the placebo-assigned patients with angina developed a stroke compared with 5% of the placebo-assigned patients without angina.

Thus, silent cerebral infarction is frequently seen in asymptomatic patients with atrial fibrillation. Age, history of hypertension, active angina, and elevated mean systolic blood pressure were associated with silent infarction at entry. The sample size was too small to determine whether warfarin had an effect on the incidence of silent infarction during the trial. Active angina at baseline was the only significant independent predictor for the later development of symptomatic stroke. From this study, questions remain whether multiple silent infarcts lead to cognitive dysfunction and subtle neurological deficits in patients with atrial fibrillation.

This clinical problem was investigated further by determining if there was an association between dementia and cognitive impairment and atrial fibrillation in 6584 patients aged 55 to 106 years. These individuals were participants in the Rotterdam Study, a population-based, prospective cohort investigation of chronic diseases in the elderly. A significant positive association of both dementia and impaired cognitive function with atrial fibrillation was found. The odds ratios, adjusted for age and sex, were 2.5 (95% CI, 1.4-2.7) and 1.7 (95% CI, 1.2-2.5) for dementia and impaired cognitive function, respectively. A history of stroke did not account for this finding, endorsing the notion that although cerebral infarctions in patients with atrial fibrillation may frequently remain clinically silent, they can result in dementia.34

The location of silent cerebral infarcts in nonrheumatic atrial fibrillation patients remains controversial. Asymptomatic infarctions were commonly found to be cortical in the patients with atrial fibrillation and in the white matter or deep structures in control subjects35 of one study. In another study, however, the opposite was found.36

The Importance of Monitoring

The SPAF III study23 and the CARS study41 used fixed doses of warfarin in their warfarin/aspirin arms—not INR adjusted—and failed to show benefit because the average INRs were below the therapeutic range. On the other hand, the SPINAF study,20 as well as the other studies,16-19,22,23 used a rigorous monitoring regimen. The SPINAF study demonstrated a 79% reduction in stroke rate among the warfarin-randomized patients without an increase in bleeding complications. Patients began taking 4 mg/d of warfarin, with a goal of maintaining the prothrombin time ratio (PTR) within 1.2 to 1.5 (INR, 1.4-2.8). Monitoring was performed weekly during a 12-week induction period and monthly thereafter during a maintenance period for a total follow-up of 36 months. Patients whose PTR was greater than 1.5 had their warfarin reduced by 1 mg/d, while patients whose PTR was less than 1.5 had their dose increased by 1 mg/d if the low PTR persisted for 2 consecutive visits.

In the SPINAF study, 260 patients were randomized to warfarin. Because of temporary and permanent withdrawals from study medication, the number of patients for whom PTRs were available varied from 234 at 1 week following randomization to 29 at the 36-month visit.42 During the induction period, the proportion of patients whose PTRs were in the desired range increased from 30.2% at 1 week to 67.6% at 12 weeks. The proportion of patients requiring a dose adjustment decreased from 56% during the early part of the induction period to 18% at the end. The mean (SD) dose increase was 0.45 (0.27) mg; the decrease was 0.58 (0.51 mg). During the 34 monthly visits in the maintenance period, the mean (SD) proportion of patients whose PTRs were within 1.2 to 1.5 was 57.3% (6.5%). The mean (SD) dose increase over the 34 visits was 0.45 (0.48) mg, with the by-visit mean increase ranging from 0.07 to 3.21 mg. The mean decrease was 0.82 (1.06) mg.

Thus, low-dose anticoagulation with warfarin in outpatients is simple to initiate using a dosage estimated to be that required for maintenance: 4 mg/d for patients younger than 70 years and 3 mg/d for older patients. Monitoring is essential. Considerable dose adjusting is required to keep patients within the therapeutic range, particularly during the initiation phase. Dose adjustments of 1-mg increments or decrements is advised. Fixed-dosage regimens are unlikely to result in patients remaining within the desired therapeutic range. Reliable monitoring in selected patients may be achieved using devices designed for home use.43-45

REFERENCES

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