 editorial comment

stroke prevention in atrial fibrillation trial

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the increasing recognition of the high risk of embolic stroke and other systemic emboli in patients with nonrheumatic atrial fibrillation, the widespread experience with lower-intensity warfarin regimens, and the extensive evidence for the efficacy of aspirin in a variety of vascular diseases led to the conduction of seven large trials of warfarin, four of which also included an evaluation of aspirin. Three of these trials have been published,1-4 and a fourth is in press.5 The Stroke Prevention in Atrial Fibrillation (SPAF) trial6 is reported in this issue of Circulation, and comment on the results is timely.

the SPAF investigators evaluated both warfarin and aspirin among patients with nonrheumatic atrial fibrillation. The study examined two groups of patients defined on the basis of their eligibility for warfarin therapy. The 627 patients in group 1 were judged by their physicians to be eligible for warfarin therapy and were randomized equally to open-label warfarin (prothrombin time, 1.3-1.8×control; INR, 2.8-4.5) or double-blind to aspirin (enteric coated, 325 mg daily) or matching placebo. The 703 patients in group 2 were considered ineligible for warfarin therapy and were randomly allocated in double-blind fashion to aspirin (enteric coated, 325 mg daily) or matching placebo.

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the patients were followed for a mean of 1.3 years, with the principal outcome being the composite of ischemic stroke or systemic embolism. Among the group 1 patients, by comparison with placebo, the rate of the primary outcomes among the warfarin-treated patients was reduced from 7.4% to 2.3% per year (absolute reduction, 5.1% per year; risk reduction, 67%; p=0.01). Among the group 1 and 2 patients, by comparison with placebo, the rate of primary outcomes among the aspirin-treated patients was reduced from 6.3% to 3.6% (absolute reduction, 2.7% per year; risk reduction, 42%; p=0.02). For the present, the investigators have not provided comparative outcome data between the patients assigned to warfarin versus aspirin in group 1, although the statement is made that the differences are not statistically significant. The investigators continue to follow group 1 patients assigned to warfarin and placebo, and additional patients have entered the ongoing trial randomly assigned to warfarin or aspirin but not placebo.

how should physicians incorporate these results into their management of patients with atrial fibrillation? Analysis of this study alone and in the context of other published trials points to a clear role for warfarin but a less certain role for aspirin.

the study subjects in the SPAF trial appear to be representative of the patients cared for by most physicians. They were both inpatients and outpatients, assembled by review of electrocardiographic and Holter logs, and by direct and self referral. There was a preponderance of men (71%) but when the patients from Veterans Administration hospitals were excluded (25% of subjects), the proportion of men was only 61%. The mean age was 67 years. The proportions of patients with angina, previous myocardial infarction, and previous stroke/transient ischemic attack (TIA) were relatively low.

hypertension was present in about half of the patients, definite congestive heart failure in one fifth, and left atrial dimension on two-dimensional echocardiogram more than 5 cm in one fourth. About two thirds of patients had atrial fibrillation for 1 year or more, and about two thirds had constant as opposed to intermittent atrial fibrillation. The distributions of all important baseline characteristics were not significantly different among the various treatment groups.

of 18,376 patients initially found to have atrial fibrillation, 7.2% were eligible for the evaluation of aspirin and 3.8% were eligible for the evaluation of warfarin, small proportions even by the standards of current large trials in vascular disease. Many of the exclusions were administrative in nature or because patients required antithrombotic therapy, but a significant proportion was excluded because of concerns about possible hemorrhagic complications. Although the study results may well be applicable to many of the excluded patients, the very low rates of bleeding by comparison with some other studies suggests that the selection process produced patients at low bleeding risk, and these rates could be higher in a general population setting.

the therapeutic regimens appeared to be entirely practicable and achievable. Patients received war-
farin in a mean dose of 4.8 mg/day to maintain monthly prothrombin times within a target range of 1.3–1.8×normal (INR, 2.0–4.5), a realistic goal that was achieved 71% of the time. Compliance with follow-up visits, study medications, and prothrombin determinations was high. The dose of aspirin was 325 mg daily of an enteric-coated preparation. Withdrawals from therapy for reasons other than study outcomes were rather uncommon, occurring in only 11.2%, 5%, and 6.6% of patients assigned to warfarin, aspirin, and placebo, respectively.

Although the authors justify their choice of an open-label design for warfarin therapy, a double-blind design might have been feasible, as was used in the Canadian Atrial Fibrillation (CAFA) study. The primary outcome constellation of ischemic stroke or systemic embolus required judgments by clinicians who could have been influenced by expectation biases (i.e., a tendency to underreport certain events in warfarin patients and perhaps to overreport them in the aspirin/placebo groups). Such expectation biases could also have influenced the reporting of relatively subjective events such as TIA and nonfatal side effects. All patients were followed to completion of the study, all important outcomes and adverse events were reported, and the outcome comparisons were made using the intention-to-treat principle. The principal outcome, a composite of ischemic stroke or systemic embolism, was significantly reduced by warfarin compared with placebo. The outcome of greatest clinical impact, that of disabling ischemic stroke or vascular death, was reduced 54% (p = 0.11), an absolute reduction of 2.6% per year.

The net patient benefit in this trial can be evaluated from an analysis of the absolute rates of reduction of the principal outcomes in relation to the major side effects. The major complications on warfarin were remarkably few and were all bleeding events (1.5% per year total and 0.4% per year with residua). Bleeding also occurred among placebo patients in group 1, with an absolute decrease on warfarin of 0.1% per year for all major bleeding and an increase of 0.4% per year for bleeding with residua. Hence, for 1,000 patients similar to those randomized to group 1 of this study, the physician could anticipate an annual prevention of 51 occurrences of ischemic stroke or systemic embolism, or 26 occurrences of disabling stroke or vascular death, with an excess occurrence of four bleeds with residua. The risk/benefit ratio is clearly in favor of warfarin therapy, an observation of great clinical importance.

The principal outcome was also reduced by aspirin compared with placebo in groups 1 and 2 (risk reduction, 42%; p = 0.02). The absolute reduction of 2.7% per year was considerably less marked than that observed for warfarin. The outcome of disabling stroke or death was reduced 22% by aspirin (p = 0.33), an absolute reduction of about 1% per year. By comparison with placebo, with aspirin there was an absolute decrease of major bleeding of about 0.5% per year and an absolute increase of 0.5% per year for bleeds with residua. Hence, for 1,000 patients of the type entered in groups 1 and 2, the practitioner might hope to observe 27 fewer occurrences of ischemic stroke or systemic embolus, or alternatively, 10 fewer occurrences of disabling stroke or vascular death at a cost per year of five more bleeds with residua. The risk/benefit ratio favors the use of aspirin but the benefit is much less marked than is that for warfarin. However, the warfarin and aspirin were evaluated in two different populations, and no direct comparison within group 1 patients is available yet.

Before making suggestions for clinical approaches, it would be wise to take into account the evidence from similar trials, of which there are two published and one in press. The Danish AFASAK study1 randomly allocated 1,007 patients to warfarin, aspirin, or placebo. The principal outcome was the composite of TIA, ischemic stroke, and systemic embolism among patients not permanently withdrawn from therapy. The observed reduction for warfarin compared with placebo was 64%, an absolute risk reduction of 3.5% per year (p < 0.05). A subsequent report of an analysis by intention to treat, excluding TIA and minor stroke, indicated a risk reduction of about 50% (p < 0.05), an absolute reduction of about 1.5% per year. The criteria for major bleeding are not directly comparable between AFASAK and SPAF, making exact comparisons difficult, but overall, the risk/benefit for stroke and systemic embolism in relation to major bleeding is less marked in the AFASAK study. There was no observed benefit of aspirin in the AFASAK study.

The Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF)4 allocated 420 patients to open-label warfarin versus placebo. The principal outcome was a composite of ischemic stroke and systemic embolism analyzed by the intention-to-treat principle. Mean follow-up was 2.2 years, and the observed reduction of ischemic stroke by warfarin compared with control was 86%, equivalent to an absolute risk reduction of 2.6% per year (p = 0.0022). Major bleeding plus transfusion was increased by an absolute amount of about 0.4% per year among the warfarin patients, although the definitions are different from those in the AFASAK and SPAF studies.

Practitioners should interpret the final results of the SPAF trial in the context of the epidemiological evidence for the risk of stroke and systemic emboli among such patients and of the data from all available clinical trials. A patient over the age of 50 years with chronic atrial fibrillation has an annual stroke risk in the range of 5%, and this may be substantially reduced with a conservative-dose warfarin regimen. The risk of bleeding with such regimens is low, the absolute increment of major bleeding being under 1% per year, and of fatal bleeding much lower. Hence, for every 1,000 patients treated with warfarin, the expectation is prevention of 15–50 occurrences per year of ischemic stroke or systemic emboli and
somewhat less reduction of disabling stroke or vascular death at a cost of about five major bleeds per year. The risk/benefit ratio appears to be very much in favor of warfarin therapy although persisting hemorrhagic risk necessitates prudent institution of such therapy.

The available data are based on rather short follow-ups of patients with chronic disease. On the other hand, the epidemiological data suggest a relatively constant annual rate of stroke after the first year of onset of atrial fibrillation, so that a sustained favorable risk/benefit ratio of warfarin therapy may be anticipated.

The population most likely to benefit appears to be patients with chronic atrial fibrillation who are over the age of 50 years and do not have specific contraindications to chronic oral anticoagulation therapy. Young patients with no evidence of cardiac abnormalities apart from atrial fibrillation (lone atrial fibrillation) are at very low risk of stroke and systemic emboli; they were excluded from warfarin evaluation in SPAF and were rare in the AFASAK study (mean age, 74.2 years) and the BAATAF study (15% of patients under age 60 years). Patients with intermittent paroxysmal atrial fibrillation have a lower risk of emboli than those with chronic atrial fibrillation.8 Such patients were excluded from AFASAK but comprised 16% of those in BAATAF and 34% of those in SPAF. The relative and absolute benefits of warfarin remain uncertain in such patients.

The most problematic disparity among the published studies is in regard to aspirin. The AFASAK study observed a statistically insignificant reduction in the principal outcome of TIA, ischemic stroke, or systemic embolus, and in the outcome of disabling stroke or vascular death analyzed by intention to treat. The results with aspirin observed in the AFASAK trial could be related to the lesser dose of aspirin (75 mg versus 325 mg daily), and might also have resulted from the higher mean age of the patients (74 versus 67 years). The latter possibility is supported by a subgroup analysis from the preliminary report of the SPAF study, indicating that the benefit of aspirin was confined to patients under the age of 75 years.3 The higher proportion of congestive heart failure patients in AFASAK compared with SPAF (50% versus 15%) may also have been a factor. There clearly are patients who may benefit from aspirin, although among these patients the benefits are more modest than among the warfarin-treated patients. On the other hand, the group 1 and 2 patients in the SPAF trial differ in several respects, so that no direct comparison of warfarin and aspirin is available yet. It is likely that for the present, aspirin therapy should be reserved for patients with contraindications to warfarin and for those with a low risk of vascular events (i.e., lone atrial fibrillation and possibly paroxysmal atrial fibrillation in the young patient). The results of SPAF II and of other trials evaluating both warfarin and aspirin should provide additional evidence to clarify the relative benefits and risks of warfarin and aspirin among patients with nonrheumatic atrial fibrillation.

References

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