EDITORIAL COMMENT
Reconsidering Combined Antiplatelet and Anticoagulant Therapy in Atrial Fibrillation*

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With the publication in 1989 of the first large randomized controlled trial of warfarin in atrial fibrillation (1), the role of anticoagulation for preventing stroke in this arrhythmia became established. Subsequent trials, published during the following decade, confirmed the efficacy of the coumarin anticoagulants and demonstrated that stroke risk was a function not only of the arrhythmia but also of the associated underlying heart disease. Also shown was a narrow window for warfarin therapy above which serious bleeding increased and below which efficacy was reduced (2). The results of trials directly comparing aspirin with coumarin anticoagulation suggested that aspirin may have a modest effect in reducing stroke and was probably associated with a lesser risk of intracranial bleeding (2). However, the magnitude of any aspirin effect in atrial fibrillation is relatively small, and it is not an adequate substitute for warfarin for stroke prevention.

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Atrial fibrillation is a disorder of older patients, and the elderly often have comorbidities that may increase the bleeding risk of long-term warfarin use. With this in mind, combinations of fixed low-dose warfarin plus aspirin were explored in the hope that bleeding would be reduced while reducing stroke risk to a similar degree as adjusted-dose warfarin. This hypothesis was resoundingly disproved by the Stroke Prevention in Atrial Fibrillation (SPAF) III investigators, who found a four-fold greater stroke risk among patients with atrial fibrillation who were treated with minidose warfarin (mean international normalized ratio [INR] 1.3) and 325 mg of aspirin daily compared with those receiving adjusted-dose warfarin with a mean INR of 2.4 (3). A subsequent well-designed case-control study confirmed that the optimal INR for stroke reduction was 2.0 and noted a doubling and tripling of stroke risk as the INR decreased to 1.7 and 1.5, respectively (4). These observations seemed to herald the death knoll for a role of antiplatelet agents in preventing stroke for the majority of patients with atrial fibrillation.

With the publication of the National Study for Prevention of Embolism in Atrial Fibrillation (NASPEAF), in this issue of the Journal, Pérez-Gómez et al. (5) have challenged this negative view of antiplatelet agents. Following in the footsteps of investigators who demonstrated a highly significant benefit of adding aspirin to therapeutic warfarin in patients with mechanical valves (6), they performed an open-label, unblinded but randomized comparison of the antiplatelet agent triflusal alone, acenocoumarol alone, or the combination of the two drugs. Acenocoumarol is a vitamin K antagonist commonly used in Europe, whereas triflusal is a less widely used antiplatelet agent that is structurally related to aspirin. Like aspirin, triflusal is an inhibitor of platelet arachidonic acid metabolism, resulting in an irreversible inhibition of platelet cyclooxygenase. However, unlike aspirin, it has little effect on vascular endothelial arachidonic acid metabolism and, hence, it does not affect prostacyclin synthesis (7). In clinical trials, it was consistently associated with a lower risk of bleeding than aspirin (8–10), and observational studies suggest less risk of gastrointestinal bleeding than that which occurs with aspirin (11).

In the currently reported trial, patients were divided into intermediate-risk and high-risk groups for thromboembolism, with the high-risk group defined as patients with either a previous neurologic event or the presence of mitral stenosis. After stratification, subjects were randomized to adjusted-dose acenocoumarol alone (target INR 2 to 3) or to 600 mg of triflusal daily plus acenocoumarol with a target INR of 1.25 to 2.0 in the intermediate-risk group and 1.4 to 2.4 in the high-risk group. A third arm was included in the intermediate-risk group consisting of triflusal 600 mg alone. The median INR for the combination therapy in the intermediate- and high-risk groups was 1.93 and 2.17, respectively. Combined therapy resulted in a statistically significant lower primary event rate in both the high- and intermediate-risk groups and demonstrated the benefits of triflusal therapy added to acenocoumarol in patients with moderate-to-high risk of embolic events from atrial fibrillation. Although severe bleeding, defined as bleeding requiring hospital admission, transfusion, or surgery, occurred more commonly in the arm receiving combined therapy, 9 of the 14 intracranial hemorrhages occurred in the group receiving anticoagulation alone.

The NASPEAF is unique in including patients with mitral stenosis because as all large previous trials of antithrombotic therapy in atrial fibrillation excluded patients with valvular disease because of the concern of a disproportionately high risk of stroke. The NASPEAF data, along with the results of a recently published small trial (12), provide important information referable to mitral stenosis. Among all patients receiving anticoagulation with a target INR of 2 to 3, the stronger predictor of an end point was the presence of a previous embolism rather than the presence of mitral stenosis, thereby underscoring the importance of
vigorous antithrombotic therapy among patients with a prior atrial fibrillation-related stroke. The findings also validate consensus recommendations extrapolated from trials of nonvalvular atrial fibrillation, that warfarin anticoagulation in patients with atrial fibrillation and mitral stenosis should be targeted to an INR of 2.0 to 3.0 (13).

Do the NASPEAF data support the benefit of combining antiplatelet therapy with coumarin anticoagulation targeted to a slightly lower INR than the current recommendation of 2.0 to 3.0? Based on their interpretation of the results of this study, Pérez-Gómez et al. (5) suggest that, “an INR of 2, considered the lower limit of safety during anticoagulation therapy, is not applicable to patients on combined therapy.” In my opinion, this conclusion is premature. Although in the high-risk group receiving combination therapy, 39% of INR measurements were <2.0, the median INR for this group was 2.17, and 21% of INR measurements in the standard anticoagulation arm were also <2.0. We do not, however, know how much lower than 2.0 these values decreased, how much of the time any individual patient’s measurements was less than this value, nor what the INR was at the time of an embolic event. In the absence of this information to evaluate the authors’ claim of safety of a lower INR than is recommended for coumarin anticoagulation alone, it is prudent to still maintain an INR of at least 2.0 in a coumarin-antiplatelet combination.

Are the results of NASPEAF applicable to warfarin and aspirin, the respective anticoagulant and antiplatelet agents most commonly used in the U.S.? Warfarin and acenocoumarol are both vitamin K antagonists, and clinical trials using either of these agents show similar benefits for a similar prolongation of INR. Thus, it is reasonable to consider data obtained with either of these two agents as interchangeable. In contrast, trifusul and aspirin differ from one another despite a structural relationship (7). Several clinical trials have compared the two agents, including studies in patients with recent myocardial infarction (10) and stroke or transient ischemic attack (8,9). A double-blind trial of 600 mg of trifusul versus aspirin 300 mg daily, started within 24 h of myocardial infarction and continued for 35 days, found no significant difference in a combined end point of death, nonfatal myocardial infarction, or nonfatal cerebrovascular events, but significantly fewer central nervous system bleeding episodes occurred in trifusul-treated patients (10). In a 431-patient pilot trial for the prevention of stroke after an episode of cerebral ischemia, the two drugs were similar in efficacy (9), and in a larger trial of 2,113 patients with recent cerebrovascular events, no benefit of trifusul over aspirin was found when a combined end point of nonfatal ischemic stroke, acute myocardial infarction, or vascular death was evaluated (8). However, major hemorrhage (defined as that requiring hospital admission and/or transfusion) was significantly lower in the trifusul group, leading to an estimate that the substitution of trifusul for aspirin in such patients would result in 24 fewer major hemorrhagic events per thousand patients treated than would occur if 325 mg of aspirin were used (8).

It is unfortunate, although understandable, that there was not a warfarin-aspirin arm in NASPEAF, but it appears reasonable, given their equivalent efficacy in other cardiovascular diseases, to conclude that aspirin may reduce ischemic stroke risk if combined with therapeutic warfarin in patients with atrial fibrillation. Indeed, this combination has been effective in patients with prosthetic valves (6). However, based on the slight but consistently greater bleeding risk of aspirin over trifusul, might the higher bleeding risk encountered with patients on aspirin offset any benefit of the combination? In the trials in which trifusul has been compared with aspirin, the aspirin dose was usually 325 mg, whereas the addition of 75 mg of aspirin to warfarin in a recent postmyocardial infarction trial did not increase the bleeding risk compared with warfarin therapy alone (14). In a meta-analysis of trials of warfarin and aspirin for patients with prosthetic heart valves (6), the combination of warfarin and aspirin was more effective in preventing thromboembolism than was warfarin alone, and low-dose aspirin (<100 mg daily) was no less effective than higher doses. Furthermore, there appeared to be a lesser risk of bleeding with aspirin when used at ≤100 mg daily in conjunction with warfarin compared with the higher dose combination, and there was no excess in major bleeding over warfarin alone in two large trials using 100 mg combined with warfarin (6).

Thus, ≤100 mg of aspirin has an equivalent efficacy in patients with cardiac disease compared with higher aspirin doses, and aspirin is not inferior to trifusul in head-to-head comparisons. Aspirin appears to be a relatively safe drug to add to warfarin with a target INR of 2 to 3, and the combination is of demonstrable benefit in preventing thromboembolism from mechanical valves. Based on these data and until more direct data are available, the clinician can, in my opinion, extrapolate from the NASPEAF to justify the addition of aspirin to therapeutic doses of warfarin in selected patients with atrial fibrillation. One such group would be those with recurrent embolic events despite adequate warfarin therapy. Others would be patients with atrial fibrillation and a prior stroke or transient ischemic attack, even if it occurred when the patient was not on antithrombotic therapy, because such patients are at high risk of a recurrent events (15) and are imperfectly protected by coumarin anticoagulation alone (5). For other patients, the potential risk-benefit is less clear, and we will have to await either a trial of the combination of therapeutic warfarin and low-dose aspirin or for the more widespread availability of trifusul.
REFERENCES


