Combining Aspirin With Oral Anticoagulant Therapy
Is This a Safe and Effective Practice in Patients With Atrial Fibrillation?

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In persons with cerebral ischemia caused by atrial fibrillation (AF) and high risk of stroke based on an overall score of a validated risk stratification scheme such as CHADS2*, adjusted-dose warfarin is recommended for those who have no clinically significant contraindication.1,2 When there is AF, adjusted-dose warfarin is estimated to reduce the risk of stroke by about 60% or more and by about 45% more than aspirin.1 The combination of adjusted-dose warfarin plus aspirin administered to AF patients may offer theoretical advantages such as enhanced stroke prevention efficacy in high-risk persons or improved protection against myocardial ischemic events in those who have coronary artery disease or diabetes.3 The recently published American Heart Association/American Stroke Association recurrent stroke prevention guideline suggests, however, no data indicate that either increasing the intensity of oral anticoagulation or add-on antiplatelet therapy provides further ischemic protection in AF patients.2 In a post hoc analysis, the Stroke Prevention Using an ORal Thrombin Inhibitor in atrial Fibrillation (SPORTIF) investigators studied the risks and benefits of combining aspirin with oral anticoagulant therapy in patients with AF.3

SPORTIF Trial Design
SPORTIF III and V trials were designed to determine whether the direct oral thrombin inhibitor ximelagatran (36 mg twice daily) was noninferior to vitamin K antagonist therapy with adjusted-dose warfarin (international normalized ratio 2.0 to 3.0) for prevention of stroke and systemic embolic events in high-risk persons with nonvalvular AF.3 The SPORTIF studies were multicenter, randomized trials. SPORTIF III was open-label and carried out in Europe, Asia, and Australasia, and SPORTIF V was double-blinded and carried out in the US and Canada. The primary outcome in both studies was the composite of ischemic and hemorrhagic strokes and systemic embolic events. Myocardial infarction was among the secondary events. Bleeding was considered major (fatal, involving a critical anatomical site, or overt and associated with a reduction in hemoglobin of 20 g/L or transfusion of at least 3 U of blood) or minor (all other bleeding).

To be eligible for the SPORTIF trials, patients could not require continuous aspirin treatment over 100 mg/d or any other antithrombotic treatment. Aspirin administration was discouraged and was not part of the randomization treatment assignment. Aspirin use was recorded as a concomitant medication and concurrent when taken at least 50% of the time. This post hoc analysis was an on-treatment approach which censored events occurring after 30 continuous days or 60 total days off study treatment except in the case of cardioversion.

A total of 7329 patients were enrolled in SPORTIF III and V. For this analysis, data were available for 7304 patients. Aspirin was administered to 531 patients in the ximelagatran treatment arm and 481 in the warfarin treatment arm. Ximelagatran alone was given to 3120 and warfarin alone to 3172 patients. The average treatment exposure was 16.5 months.3

SPORTIF Post Hoc Analysis: What Happened When Aspirin Was Added to Ximelagatran or Warfarin?

Baseline Characteristics
There were many differences in baseline characteristics among those receiving aspirin in conjunction with anticoagulant therapy compared with those receiving antiocoagulant therapy alone. Those taking aspirin were more likely to be men or Asian, have a history of smoking, diabetes mellitus, coronary heart disease, prior stroke or transient ischemic

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*CHADS2 scheme is based on medical history of: C=congestive heart failure, H=hypertension, A=age >75 years, D=diabetes mellitus, and S2=stroke or transient ischemic attack. One point is assigned for each of C, H, A, and D, and 2 points are assigned for each of stroke or transient ischemic attack. For patients with a score of 0, aspirin (75 to 325 mg/d) is recommended; a score of 1, warfarin or aspirin may be prescribed; and a score ≥2, warfarin is recommended. All nonvalvular AF patients with stroke or transient ischemic attack should be considered for warfarin administration.1

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attack, and left ventricular dysfunction but were less likely to drink alcohol and had slightly lower systolic and diastolic blood pressures.³

Primary and Secondary Outcomes
Event rates per patient-year did not differ significantly (P<0.05) for the primary outcomes stroke or stroke/systemic embolism in the ximelagatran or ximelagatran plus aspirin treatment groups. Stroke or stroke/systemic embolism ranged from 1.2%–1.4% to 1.6%–1.7% for those taking ximelagatran versus ximelagatran plus aspirin, respectively. The myocardial infarction and death rates did not differ significantly by treatment group either (1.0%–2.3% to 1.4%–3.0%, respectively). For the warfarin versus aspirin plus aspirin treatment groups, the event rates for stroke or stroke/systemic embolism ranged from 1.5%–1.55% to 1.7%–1.7%, respectively, and the event rates for myocardial infarction and death were 1.0%–2.5% to 0.6%–2.6%, respectively. Again, there was no statistically significant difference between the event rates with or without aspirin therapy.

Safety
Major differences began to emerge when safety was considered. Although major bleeding events did not differ between the ximelagatran versus ximelagatran plus aspirin treatment groups (1.9% versus 2.0%, P=0.83), the combination of major/minor bleeds differed with more bleeds occurring in the ximelagatran plus aspirin treatment group (39.4% versus 31.45%, P<0.01). In the warfarin treatment groups, both major (3.9% versus 2.3%, P=0.01) and major/minor bleeds (62.8% versus 36.8%, P<0.01) were more common with warfarin plus aspirin versus warfarin alone. When baseline differences were adjusted for, there was a significant interaction between aspirin and warfarin or ximelagatran with respect to bleeding, which was especially high for warfarin. The increased risk of major bleeding with warfarin plus aspirin showed a hazard ratio of 1.58 (95% CI, 1.02 to 2.49; P=0.05), yet this was not observed with the combination of ximelagatran plus aspirin.

Discussion
In this study patients taking aspirin were generally at higher risk of cardiovascular events. Furthermore, the combination therapy of aspirin with either ximelagatran or warfarin did not reduce the risk of stroke, systemic embolism, or myocardial infarction, but the addition of aspirin to warfarin or ximelagatran was associated with increased risk of bleeding, which was especially high when aspirin and warfarin were combined.

One must be cautious, however, when interpreting these efficacy and safety signals because there are several key potential study limitations. For example, the results are based on post hoc analysis. Such analysis is generally believed to be of value to assist in the formulation of hypotheses but not to test them because play of chance may be increased when the comparisons are not randomized, and there may be uncontrollable and uncontrollable confounding.⁴ In the African American Antiplatelet Stroke Prevention Study (AAASPS), a published subgroup analysis from the Ticlopidine Aspirin Stroke Study (TASS) was used in part to establish AAASPS sample-size calculations.⁵,⁶ TASS data suggested that ticlopidine would be substantially more efficacious than aspirin in recurrent stroke prevention.⁵ When the hypothesis was carefully tested in the main phase National Institute of Neurological Disorders and Stroke/National Institutes of Health (NINDS/NIH)-funded clinical trial, this did not turn out to be the case because we found no significant difference between the ticlopidine and aspirin treatment groups for the primary outcome of stroke, myocardial infarction and vascular death in African Americans.⁵ In addition, AAASPS was stopped prematurely based on futility analyses. Had it been continued to completion, however, there was a 40% to 50% likelihood of aspirin being significantly better in reducing the risk of recurrent fatal or nonfatal stroke.⁵ Challenges to subgroup analyses such as these⁵,⁶ have been reviewed by Lagakos⁷ and Pfeffer and Jarcho⁸ in the context of a recent cardiovascular prevention trial which featured combination antiplatelet therapy.

Other potential pitfalls of the post hoc analyses carried out by Flaker et al in the current article of interest⁹ include imbalances in baseline characteristics, nonrandomized study design in relation to aspirin administration, the relatively small numbers of aspirin users in the study, the relatively small number of outcome events in some of the comparison subgroups, and the fact that study investigators discouraged use of aspirin.

In February 2006, AstraZeneca announced the withdrawal of ximelagatran from the market and termination of its development based on concerns over safety.⁹ Aspirin, other antiplatelet agents, and oral vitamin K antagonists are available in the US and other countries for cardiovascular disease prevention. Either aspirin or warfarin when given alone and according to standard guidelines is safe and effective for stroke prevention.¹,²,¹⁰,¹¹ Whereas the combination of aspirin plus warfarin holds theoretical advantages in stroke prevention, this combination therapy cannot be recommended presently for routine use based on available scientific data which do not substantially support its efficacy and raise concerns over its safety. Similar to the combination of aspirin plus clopidogrel, the combination of an antiplatelet agent and an oral anticoagulant in stroke patients seems to increase the risk of intracranial hemorrhage.¹¹ Avoiding these combinations, controlling blood pressure, and maintaining an international normalized ratio at 3.0 or below when warfarin is administered may reduce risk of brain hemorrhage.¹¹ Furthermore, we must keep in mind that certain populations may be at high risk of brain hemorrhage even when these agents are given individually,¹⁰–¹² and additional study to better understand this phenomenon may prove clinically useful. Aspirin, however, is recommended concurrently for ischemic coronary disease during oral anticoagulant treatment in doses up to 162 mg/d (Class IIA, Level of Evidence A).²

Disclosures
Dr Gorelick receives honoraria as a consultant to AstraZeneca, Bayer, and Boehringer Ingelheim, as a study steering committee member for Bayer, and as a lecturer for Boehringer Ingelheim.
References

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