

# Risks and benefits of combining aspirin with anticoagulant therapy in patients with atrial fibrillation: An exploratory analysis of stroke prevention using an oral thrombin inhibitor in atrial fibrillation (SPORTIF) trials

Greg C. Flaker, MD,<sup>a,i,j</sup> Michael Gruber, MS,<sup>b</sup> Stuart J. Connolly, MD,<sup>c,i,j</sup> Steven Goldman, MD,<sup>d,i</sup> Sandra Chaparro, MD,<sup>a</sup> Alec Vahanian, MD,<sup>c,k</sup> Matti O. Halinen, MD,<sup>f,i,j</sup> Jay Horrow, MD,<sup>g,l</sup> and Jonathan L. Halperin, MD<sup>h,k</sup> the SPORTIF Investigators *Columbia, MO; Madison, WI; Hamilton, Ontario, Canada; Tucson, AZ; Paris, France; Kuopio, Finland; Wilmington, DE; and New York, NY*

**Background** Aspirin is used in combination with anticoagulant therapy in patients with atrial fibrillation (AF), but evidence of additional efficacy is not available.

**Methods** We compared ischemic events and bleeding in the SPORTIF III and IV randomized trials of anticoagulation with warfarin (international normalized ratio 2-3) or fixed-dose ximelagatran. Low-dose aspirin (<100 mg/d) was allowed based on prevailing guidelines.

**Results** The 14% of patients receiving aspirin more often had diabetes (27.5% vs 23%,  $P < .01$ ), coronary artery disease (69% vs 41%,  $P < .01$ ), previous stroke or transient ischemic attack (26% vs 20%,  $P < .01$ ), and left ventricular dysfunction (41% vs 36%,  $P < .01$ ). Addition of aspirin to either warfarin or ximelagatran was associated with no reduction in stroke or systemic embolism. Major bleeding occurred significantly more often with aspirin plus warfarin (3.9% per year) than with warfarin alone (2.3% per year,  $P < .01$ ), aspirin plus ximelagatran (2.0% per year), or ximelagatran alone (1.9% per year). The rate of myocardial infarction with aspirin and warfarin (0.6% per year) was not significantly different from that with ximelagatran alone (1.0% per year), warfarin alone (1.0% per year), or aspirin and ximelagatran (1.4% per year).

**Conclusions** Aspirin combined with anticoagulant therapy was associated with no reduction in stroke, systemic embolism, or myocardial infarction in patients with AF. Aspirin combined with warfarin was associated with an incremental rate of major bleeding of 1.6% per year. No increased major bleeding occurred with aspirin and ximelagatran. These results suggest that the risks associated with addition of aspirin to anticoagulation in patients with AF outweigh the benefit. (Am Heart J 2006;152:967-73)

From the <sup>a</sup>Department of Medicine, University of Missouri-Columbia, Columbia, MO, <sup>b</sup>Department of Biostatistics, University of Wisconsin-Madison, Madison, WI, <sup>c</sup>McMaster University, Hamilton, Ontario, Canada, <sup>d</sup>Tucson Veteran's Hospital, Tucson, AZ, <sup>e</sup>Department of Cardiology, Hospital Tenon, Paris, France, <sup>f</sup>Division of Conservative Disciplines, Kuopio University Hospital, Kuopio, Finland, <sup>g</sup>AstraZeneca LP, Wilmington, DE, and <sup>h</sup>Mt. Sinai Medical Center, New York, NY.

<sup>i</sup>Drs Flaker, Connolly, Goldman, and Halinen have received research grants from AstraZeneca.

<sup>j</sup>Drs Flaker, Connolly, and Halinen are on the AstraZeneca speaker's bureau.

<sup>k</sup>Dr Vahanian and Dr Halperin are consultants to AstraZeneca.

<sup>l</sup>Dr Horrow is an employee of AstraZeneca.

Submitted April 14, 2006; accepted June 16, 2006.

Reprint requests: Greg C. Flaker, MD, 314 McHaney Hall, University of Missouri Hospital and Clinics, Columbia, MO 65212.

E-mail: flakerg@health.missouri.edu

0002-8703/\$ - see front matter

© 2006, Mosby, Inc. All rights reserved.

doi:10.1016/j.ahj.2006.06.024

Anticoagulation with warfarin is effective therapy for stroke prevention in patients with atrial fibrillation (AF),<sup>1</sup> and aspirin is protective against stroke in patients at risk for vascular events.<sup>2,3</sup> In selected populations at high risk, combining anticoagulation with antiplatelet therapy may offer additional protection against vascular events, but bleeding is increased with combination therapy, and its superior efficacy over anticoagulation alone has not been proven in patients with nonvalvular AF.

The theoretical advantage of combining oral anticoagulants and antiplatelet agents include allowing lower anticoagulation intensity to retain efficacy or reduce hemorrhagic risk, enhancing stroke-preventive efficacy for high-risk patients (such as those with prior

stroke), or bolstering protection against myocardial ischemic events in patients with AF who have coronary artery disease (CAD) or diabetes. In previous randomized trials involving patients with AF, combinations of very low intensities of anticoagulation with aspirin were no more effective in preventing stroke.<sup>4,5</sup> However, the addition of aspirin to more conventional intensities of anticoagulation reduced embolic event rates in patients with mechanical prosthetic valves,<sup>6</sup> reduced ischemic events in patients with acute coronary syndromes,<sup>7</sup> and reduced cardiovascular events and death in patients with recent myocardial infarction (MI).<sup>8</sup> The combination of aspirin with warfarin was associated with an increased risk of bleeding in each of these situations.

The SPORTIF studies provide information about the outcomes in patients treated with aspirin used in conjunction with anticoagulant medication in patients with AF. Our goals were to determine if aspirin therapy was associated with a reduction in stroke and cardiovascular events and to determine the risks of bleeding in these patients.

## Methods

The rationale, design, and main results of the SPORTIF III and V studies have been published elsewhere.<sup>9-11</sup> In brief, these randomized multicenter trials were designed to demonstrate the noninferiority of the oral direct thrombin inhibitor ximelagatran (36 mg twice daily), compared with vitamin K antagonist therapy with adjusted-dose warfarin (international normalized ratio [INR] 2-3) for prevention of all stroke and systemic embolism in high-risk patients with nonvalvular AF enrolled in 2000 and 2001. In addition to AF, these patients had hypertension, previous stroke, transient ischemic attack (TIA) or systemic embolism, left ventricular dysfunction, age >75 years, or age >65 years with CAD or diabetes mellitus as risk factors for subsequent stroke. SPORTIF III involved open-label treatment in 23 countries in Europe, Asia, and Australasia. SPORTIF V was identical in design but included double-blinded treatment assignment at centers in the United States and Canada. The results presented here represent a pooled analysis of the 2 studies because the risk factors for stroke and the key patient characteristics were clinically comparable between the trials.<sup>12</sup> Signed informed consent was required from every participant according to a protocol approved by local ethics committees and in accordance with the Declaration of Helsinki. Outcomes in both studies were subjected to blinded end point adjudication.

The primary outcome of both studies was the composite of all strokes (ischemic or hemorrhagic) and systemic embolic events according to intention-to-treat analysis. Stroke was defined as the abrupt onset of a focal neurologic deficit in the distribution of a brain artery lasting >24 hours. A deficit lasting <24 hours constituted a TIA. Local study-affiliated neurologists or stroke specialists masked to treatment assessed suspected neurologic events and submitted clinical and neuroimaging findings to an independent, blinded central events adjudication committee for review. Secondary events were also subjected to such analysis. Among these was MI, defined by at least 2 of the following criteria: (1) typical retrosternal chest pain lasting for at least 20

minutes, (2) an electrocardiogram showing changes of acute MI, and (3) cardiac enzymes elevation more than twice the upper limit of normal. Bleeding was classified as major if fatal, involved a critical anatomical site, or overt and associated with a decrease in hemoglobin level of 20 g/L or transfusion of at least 2 U of blood. Other reported bleeding that did not satisfy criteria for major bleeding was considered as minor.

Patients were excluded if they required continuous aspirin treatment in any dose over 100 mg/d or any other antithrombotic agents. The protocol discouraged aspirin, but doses up to 100 mg/d were permitted based on prevailing clinical practice guidelines.<sup>13</sup> Randomized anticoagulant drug assignment was stratified for aspirin use at entry, but aspirin administration was not randomized. Use of aspirin during the study was recorded as a concomitant medication with dates of initiation and cessation. For purposes of this analysis, patients were considered on concurrent treatment when aspirin was taken at least 50% of the time on study drug. Once a primary outcome (stroke or systemic embolism) occurred, study drug was stopped and aspirin follow-up was considered complete. Similarly, aspirin follow-up was considered complete if an MI occurred, although study medication may have continued or aspirin may have been added.

Baseline demographic variables and outcomes were compared for patients on randomized treatment alone and those taking concurrent aspirin. An on-treatment approach was used, censoring events occurring after 30 continuous or 60 total days off study treatment, except that up to 60 continuous days off study treatment was allowed without censoring for patients undergoing cardioversion. For this post hoc analysis, the Kruskal-Wallis test was used to compare continuous variables and the Pearson  $\chi^2$  was used for categorical variables. A Cox proportional hazards model for multivariable analysis used the following covariates: aspirin use (as defined), age, body mass index, systolic blood pressure, sex, race, alcohol use, pattern of AF (paroxysmal or persistent), previous stroke or TIA, and CAD. The proportionality assumption was checked using time-dependent terms for all covariates, and terms significant at the .05 level were included in the model. Adjusted results were derived from the model including both the prespecified covariates and the significant time-dependent determinants.

## Results

Of the 7329 enrolled patients (3407 patients in SPORTIF III and 3922 patients in SPORTIF V), concurrent medication logs were unavailable for 25 patients, leaving data from 7304 patients available for secondary analysis. Of these, aspirin was prescribed to 531 patients in the ximelagatran group and 481 patients in the warfarin group. Thus, the current study compared the following groups at baseline: ximelagatran ( $n = 3120$ ), ximelagatran plus aspirin ( $n = 531$ ), warfarin ( $n = 3172$ ), and warfarin plus aspirin ( $n = 481$ ). The on-treatment analysis covered an average treatment exposure of 16.5 months.

Important baseline differences between patients receiving aspirin in conjunction with anticoagulant and those taking anticoagulation alone were noted (Table I). Patients receiving aspirin were more often men (76% vs

**Table 1.** Demographic features of patients receiving ximelagatran or warfarin without aspirin compared with patients receiving aspirin >50% of days of study treatment with antithrombotic therapy

	No aspirin		Aspirin + antithrombotic therapy		P
	n = 6292		n = 1012		
	n	%	n	%	
Sex					
Male	4283	68.1	773	76.4	<.0001
Female	2009	31.9	239	23.6	
Race					
White	5840	92.8	896	88.5	<.0001
Black	111	1.8	16	1.6	
Asian	323	5.1	96	9.5	
Other	18	0.3	4	0.4	
Age (y)	70.9 + 8.9		71.3 + 8.7		.3079
Weight (kg)	85.7 + 19.9		85.8 + 20.9		.8431
BMI (kg/m <sup>2</sup> )	29.0 + 5.8		28.8 + 5.9		.1088
Smoking status					
Nonsmoker	2706	43.0	383	37.8	.0204
Ex smoker	3011	47.9	528	52.2	
Occasional	121	1.9	19	1.9	
Habitual	454	7.2	82	8.1	
Any alcohol					
No	3396	54.0	593	58.6	.0062
Yes	2895	46.0	419	41.4	
AF chronicity					
Paroxysmal	695	11.1	132	13.0	.0634
Constant	5594	88.9	880	87.0	
Diabetes mellitus					
No	4854	77.1	734	72.5	.0013
Yes	1438	22.9	278	27.5	
CAD					
No	3718	59.1	311	30.7	<.0001
Yes	2573	40.9	701	69.3	
Hypertension					
No	1461	23.2	234	23.1	.9457
Yes	4831	76.8	778	76.9	
Prior stroke/TIA					
No	5015	79.7	753	74.4	.0001
Yes	1277	20.3	259	25.6	
Prior SEE					
No	6010	95.5	967	95.6	.9599
Yes	282	4.5	45	4.4	
Systolic blood pressure (mm Hg)	135.7±17.9		133.8±19.1		<.0011
Diastolic blood pressure (mm Hg)	79.6±10.3		78.2±11.0		<.0001
Left ventricular dysfunction					
No	4037	64.2	594	58.7	.0008
Yes	2255	35.8	418	41.3	
Number of risk factors*					
0	15	0.2	2	0.2	<.0001
1	1848	29.4	197	19.5	
2	2072	32.9	298	29.4	
3	1397	22.2	277	27.4	
4	676	10.7	161	15.9	
>4	284	4.5	77	7.6	

ASA, Aspirin; BMI, body mass index; SEE, systemic embolic event.

\*Based on the following: hypertension, age >75 years, previous stroke/TIA, SEE, left ventricular dysfunction, age >65 years and CAD, and age >65 years and diabetes mellitus.

68%) and/or Asian (9.5% vs 5%), with a history of smoking tobacco (62% vs 57%) but were less likely to use alcohol regularly (41% vs 46%). The total number of

risk factors for stroke other than AF was greater in patients receiving aspirin. Those taking aspirin had a higher incidence of previous stroke or TIA (26% vs 20%),

**Table II.** Event rates per patient year of follow-up

	<b>Ximelagatran (n = 3120)</b>	<b>Ximelagatran + ASA (n = 531)</b>	<b>P</b>
Stroke	1.2% (50/4195)	1.6% (11/707)	.43
Stroke/systemic embolism	1.4% (58/4194)	1.7% (12/707)	.52
MI	1.0% (40/4193)	1.4% (10/697)	.23
Death	2.3% (95/4200)	3.0% (21/707)	.26
	<b>Warfarin (n = 3172)</b>	<b>Warfarin + ASA (n = 481)</b>	<b>P</b>
Stroke	1.5% (67/4455)	1.7% (11/642)	.71
Stroke/systemic embolism	1.55% (69/4454)	1.7% (11/642)	.78
MI	1.0% (46/4452)	0.6% (4/643)	.40
Death	2.5% (112/4464)	2.6% (17/644)	.84

Figures in parenthesis represent the number of patients with events/patient years. ASA, aspirin.

**Table III.** Bleeding rates per patient year of follow-up

	<b>Ximelagatran (n = 3120)</b>	<b>Ximelagatran + ASA (n = 531)</b>	<b>P</b>
Major bleed	1.9% (78)	2.0% (14)	.83
Major/minor bleed	31.45% (1013)	39.4% (202)	<.01
	<b>Warfarin (n = 3172)</b>	<b>Warfarin + ASA (n = 481)</b>	<b>P</b>
Major bleed	2.3% (100)	3.9% (25)	.01
Major/minor bleed	36.8% (1199)	62.8% (251)	<.01

Figures in parenthesis represent the number of patients with events. A total of 231 patients experienced at least 1 major bleeding event during the on-treatment period. Of these, 10 had >1 bleeding event: 4 had multiple bleeds of the same type and 6 had multiple bleeds involving different anatomical sites.

left ventricular dysfunction (41% vs 36%), diabetes mellitus (27.5% vs 23%), and CAD (69% vs 41%). Patients using aspirin had slightly lower systolic blood pressure (134 vs 136 mm Hg) than those not receiving aspirin.

Rates of stroke or systemic embolism (primary events) were similar in patients receiving warfarin with or without aspirin and ximelagatran with or without aspirin, ranging from 1.4% to 1.7% per year of follow-up (Table II). Of the 14 patients with hemorrhagic stroke, none were taking aspirin. The mortality rates were similar in the 4 groups of patients and ranged from 2.3% to 3% per year. The risk of MI was similar in patients receiving ximelagatran with aspirin, compared with those receiving ximelagatran alone (1.4% vs 1.0% per year,  $P = .23$ ). Similarly, no difference in risk of MI was observed in patients receiving warfarin plus aspirin (0.6% per year) compared with those taking warfarin alone (1.0% per year) (Table II).

Patients taking aspirin with either ximelagatran or warfarin developed a higher rate of bleeding (major plus minor) compared with patients receiving either anticoagulant alone (Table III). Major bleeding was

**Table IV.** Location of major bleeding

<b>Primary location of bleeding</b>	<b>Number of patient with events (no ASA, ASA)*</b>	<b>Percentage of patients with at least 1 major bleeding event†</b>
CNS bleed‡	17 (16, 1)	7.1
Subdural hematoma	21 (16, 5)	8.7
Pericardial	4 (4, 0)	1.7
Retroperitoneal	8 (6, 2)	3.3
Atraumatic intra-articular	1 (0, 1)	0.4
Intraocular	15 (12, 3)	6.2
Intraspinal	1 (1, 0)	0.4
Gastrointestinal	92 (79, 13)	38.2
Urinary	15 (12, 3)	6.2
Other	57 (45, 12)	23.7
Missing	19 (15, 4)	7.9

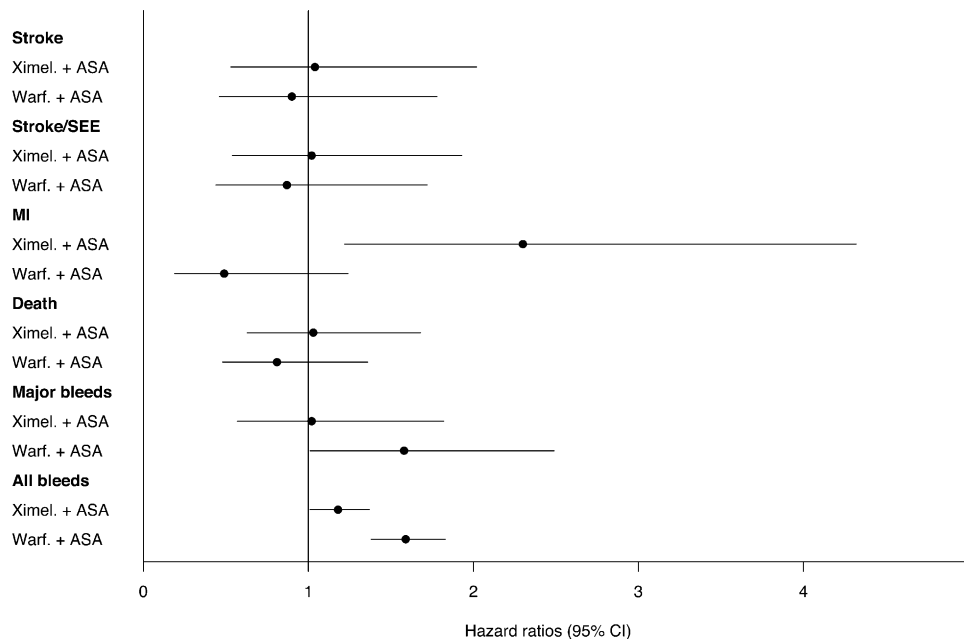
CNS, Central nervous system.

\*Numbers in parentheses are number of patients with at least 1 bleeding event of this type in the 6292 patients not taking aspirin and in the 1012 patients taking aspirin >50% of the days on study treatment.

†Percentage of the 241 patients with at least 1 major bleeding event of this type. Percentages do not add to 100% because some patients had multiple major bleeding events, some of same types and some of different types.

‡Included as primary events.

**Figure 1**



Major events occurring when aspirin is given in association with warfarin and ximelagatran. *AMI*, Acute MI; *ASA*, aspirin; *SEE*, systemic embolic event; *Warf*, warfarin; *Ximel*, ximelagatran.

significantly higher in patients receiving aspirin with warfarin (3.9% per year) than in those taking warfarin alone (2.3% per year,  $P = .01$ ). In patients receiving aspirin with ximelagatran, the risk of major bleeding was about the same as in those taking ximelagatran alone (2.0% vs 1.9% per year). Major bleeding most often involved the gastrointestinal tract (Table IV).

Because data were missing for 44 patients, the multivariable analysis was limited to data from 7260 patients. This exposed significant interaction between aspirin use and treatment with either anticoagulant for the primary end point, MI, and bleeding, and hazard ratios were calculated separately for each treatment. After adjusting for baseline differences, aspirin use during therapy with either ximelagatran or warfarin was not associated with reduced rates of either primary events or stroke as an isolated end point. With respect to bleeding, there was significant interaction between aspirin use and therapy with either warfarin or ximelagatran, with the combination of warfarin and aspirin associated with particularly high risk. The use of aspirin with warfarin was independently associated with an increased risk of major bleeding (HR 1.58, 95% CI 1.01-2.49,  $P = .05$ ), yet major bleeding was not increased by the combination of aspirin with ximelagatran. When overall (major and minor) bleeding was considered, aspirin was associated with an increased risk when given

in combination with either ximelagatran or warfarin (Figure 1).

## Discussion

This post hoc analysis involves patients given aspirin in addition to randomized anticoagulant therapy (either warfarin or ximelagatran) under a protocol that prohibited aspirin, except in limited dosage for patients considered at high risk, usually because of a clinical history of CAD. Patients taking aspirin on the advice of their physicians were therefore generally at higher risk for developing the cardiovascular events that served as end points in these studies. The combination of aspirin with either ximelagatran or warfarin was not associated with a lower rate of stroke or systemic embolism or MI in these patients, either because the additional protection afforded by aspirin against thromboembolism was insufficient to overcome this higher intrinsic risk or because of some other property of aspirin that raised the risk of ischemic events during concurrent therapy with an anticoagulant. The addition of aspirin to either warfarin or ximelagatran was associated with an increased risk of bleeding. Major bleeding increased >1.6% per year when the anticoagulant was warfarin, although the INR was closely regulated with the target therapeutic range. Major bleeding was not increased when aspirin was supple-

mentary to ximelagatran, but even this combination was associated with an increased risk of overall (major and minor) bleeding complications.

Two randomized trials have evaluated the combination of aspirin plus warfarin for stroke prevention in patients with AF,<sup>4,5</sup> and neither found a reduction in stroke compared with treatment with adjusted-dose warfarin alone (target INR 2-3). In the SPAF III study, patients with AF and at least 1 additional thromboembolic risk factor (heart failure or left ventricular fractional shortening <25%, prior thromboembolism, systolic hypertension >160 mm Hg at entry, or age >75 years in women) were randomized to adjusted-dose warfarin (target INR 2.0-3.0) or a combination of low-intensity, fixed-dose warfarin (INR 1.2-1.5, daily dose <3 mg) plus aspirin (325 mg/d). In the AFASAK 2 study, patients were randomized to warfarin (1.25 mg/d, mean achieved INR 1.05) plus aspirin (300 mg/d) or to warfarin alone (target INR 2.0-3.0). The study was stopped before completion of planned enrollment, in part because of the results of SPAF III and, thus, lacked power to detect a difference between the 2 regimens. In aggregate, the studies found adjusted-dose warfarin superior to the combination of low-dose warfarin plus aspirin (relative risk reduction 74%). This analysis of data from the SPORTIF trials expands those observations in patients with AF, as it involves combinations of aspirin and either warfarin or ximelagatran at therapeutic anticoagulation intensities. The number of stroke and systemic embolic events exceeds that in SPAF III and AFASAK 2. Although platelet-inhibitor treatment was not randomized, addition of aspirin was not associated with lower rates of stroke and systemic embolism than observed with either warfarin or ximelagatran alone.

In the AFFIRM study of 4060 patients deemed eligible for anticoagulation, addition of aspirin to anticoagulant therapy was associated with a 2-fold greater risk of major bleeding than anticoagulation alone.<sup>14</sup> The combination of aspirin with anticoagulant therapy placed patients at greater risk of intracerebral hemorrhage.<sup>15</sup> Because most strokes in warfarin-treated patients with AF occurred when the INR was subtherapeutic,<sup>16,17</sup> clinicians seeking to protect their patients against stroke should maintain adequate anticoagulation intensity by adjustment of warfarin dosage rather than add aspirin until more definitive data become available from randomized trials of combination therapy.

In the SPORTIF trials, adding aspirin to anticoagulant therapy was associated with higher rates of bleeding and no benefit in terms of preventing cerebral, systemic, or coronary ischemic events. Addition of aspirin to warfarin at lower intensities in previous studies involving patients with CAD seemed to have a salutary effect, preventing ischemic events. Among survivors of MI, aspirin (75 mg/d) combined with warfarin (target INR 2.8-4.2) showed superior efficacy for the composite end

point of death, MI, and ischemic stroke than either warfarin or aspirin given separately. After a follow-up interval of 4 years, minor bleeding was more frequent in patients receiving the combination than those on warfarin alone, but there was no increase in major bleeding.<sup>8</sup> In the ASPECT-2, study of patients with recent acute coronary events, treatment with high-intensity oral anticoagulation (INR 3-4) or aspirin with medium-intensity oral anticoagulants was more effective than aspirin alone in reducing cardiovascular events and death.<sup>7</sup> Minor (but not major) bleeding was significantly more frequent in those given the combination of aspirin (100 mg/d) plus oral anticoagulation (INR 2-2.5) than in those given monotherapy.

Other antiplatelet agents may add efficacy when used in conjunction with an oral anticoagulant for prevention of ischemic events in patients with AF. In the NASPEAF trial, triflusal (an irreversible inhibitor of platelet cyclooxygenase) was combined with acenocoumarol (a vitamin K antagonist, INR 1.25-2) and compared with acenocoumarol alone (INR 2-3) in patients at intermediate risk of stroke.<sup>18</sup> Triflusal combined with acenocoumarol at slightly higher intensity (INR 1.2-2.4) was also compared with acenocoumarol alone (INR 2-3) in patients at higher risk for stroke because of prior thromboembolism or mitral stenosis. There were no differences in severe bleeding episodes between the anticoagulant arm and the combined therapy arm, and the combination was associated with fewer vascular events (vascular death, TIA, and nonfatal stroke or systemic embolism) than acenocoumarol alone, but rates of stroke were not significantly different between groups. Other studies involving patients with AF, including the ACTIVE, are also evaluating antiplatelet agents to reduce the rate of vascular events.

The main goal of the SPORTIF program was to compare the relative efficacy and safety of the oral direct thrombin inhibitor ximelagatran with warfarin. Because aspirin was assigned to our patients at the discretion of individual physicians and not in a randomized fashion, treatment biases likely exist. Patients who received aspirin had more risk factors for stroke and MI, including a higher incidence of CAD, than those not receiving aspirin. Other factors not identified as covariates in the Cox proportional hazard model may have contributed differentially to the risk of events. As such, the results of this post hoc analysis must be considered hypothesis-generating rather than conclusive.

In summary, in this post hoc analysis, administration of aspirin with warfarin or ximelagatran to patients in the SPORTIF studies was not associated with a reduction in stroke, embolic events, or MI. The combination of aspirin plus warfarin was associated with an increase in major bleeding (1.6% per year), but the addition of aspirin to ximelagatran was not associated with increased major bleeding, although an increased risk of

minor bleeding occurred when aspirin was combined with either anticoagulant. Given the apparent risks that accrue when aspirin is added to anticoagulant therapy, clinicians seeking to prevent stroke in patients with AF might instead focus on maintaining therapeutic anti-coagulation intensity.

## References

1. Hart RG, Benavente O, McBride R, et al. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation; a meta-analysis. *Ann Intern Med* 1999;131:492-501.
2. Antiplatelet Trialists' Collaboration. Antiplatelet Trialists' Collaboration Collaborative overview of randomized trials of antiplatelet therapy-I. Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994;308:81-106.
3. Antiplatelet Trialists' Collaboration. Antithrombotic Trialists' Collaboration Collaborative meta-analysis of randomized trials of antiplatelet therapy for prevention of death, myocardial infarction and stroke in high risk patients. *BMJ* 2002;324:71-86.
4. Stroke Prevention in Atrial Fibrillation Investigators. Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation: Stroke Prevention in Atrial Fibrillation III Randomized Clinical Trial. *Lancet* 1996;348:633-8.
5. Gullov AL, Koefoed BG, Petersen P, et al. Fixed minidose warfarin and aspirin alone and in combination vs adjusted-dose warfarin for stroke prevention in atrial fibrillation. Second Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation Study. *Arch Intern Med* 1998;158:1513-21.
6. Turpie A, Gent M, Laupacis A, et al. A comparison of aspirin with placebo in patients treated with warfarin after heart-valve replacement. *N Engl J Med* 1993;329:534-9.
7. Van Es RF, Jonker JJC, Verheugt FWA, et al. for the Antithrombotics in the Secondary Prevention of Events in Coronary Thrombosis-2 (ASPECT-2) Research Group Aspirin and Coumadin After Acute Coronary Syndromes (the ASPECT-2): a randomized controlled trial. *Lancet* 2002;360:109-13.
8. Hurlen M, Abidehnoor M, Smith P, et al. Warfarin, aspirin, or both after myocardial infarction. *N Engl J Med* 2002;347:969-74.
9. Halperin JL, and the Executive Steering Committee on behalf of the SPORTIF III and V Study Investigators. Ximelagatran compared with warfarin for prevention of thromboembolism in patients with nonvalvular atrial fibrillation: rationale, objectives and design of a pair of clinical studies and baseline patient characteristics. *Am Heart J* 2003;146:431-8.
10. Executive Steering Committee, on behalf of the SPORTIF III Investigators. Stroke prevention with the oral direct inhibitor ximelagatran compared with warfarin patients with non-valvular atrial fibrillation (SPORTIF III): randomized controlled trial. *Lancet* 2003;362:1691-8.
11. SPORTIF Executive Committee, for the SPORTIF V Investigators. Ximelagatran vs. warfarin for stroke prevention in patients with nonvalvular atrial fibrillation: a randomized trial. *JAMA* 2005;293:690-8.
12. Diener H, and the Executive Steering Committee on behalf of the SPORTIF III and V Investigators. Stroke prevention using the oral direct thrombin inhibitor ximelagatran in patients with non-valvular atrial fibrillation. *Cerebrovasc Dis* 2005;21:279-93.
13. Fuster V, Ryden L, Asinger R, et al. ACC/AHA/ESC Guidelines for the management of patients with atrial fibrillation: executive summary a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society Of Cardiology Committee for Practice Guidelines and Policy Conferences (committee to develop guidelines for the management of patients with atrial fibrillation) developed in collaboration with the North American Society of Pacing and Electrophysiology. *Circ* 2001;104:2118-50.
14. Dimarco JP, Flaker G, Waldo AL, et al. Factors affecting bleeding during anticoagulant therapy in patients with atrial fibrillation: observations from the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study. *Am Heart J* 2005; 149:650-6.
15. Hart RG, Tonarelli SB, Pearce LA. Avoiding central nervous system bleeding during antithrombotic therapy: recent data and ideas. *Stroke* 2005;36:1588-93.
16. The Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med* 2002;347:1825-33.
17. Van Gelder IC, Hagens VE, Bosker HA, et al, for the Rate Control vs. Electrical Conversion for Persistent Atrial Fibrillation Study Group A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med* 2002;347: 1834-40.
18. Perez-Gomez F, Alegria E, Berjon J, et al, for the NASPEAF Investigators. Comparative effects of antiplatelet, anticoagulant, or combined therapy in patients with valvular and nonvalvular atrial fibrillation. *J Am Coll Cardiol* 2004;44:1557-66.