Disparate Stroke Rates on Warfarin Among Contemporaneous Cohorts With Atrial Fibrillation
Potential Insights Into Risk From a Comparative Analysis of SPORTIF III Versus SPORTIF V
Elaine M. Hylek, MD, MPH; Lars Frison, PhD; Lori E. Henault, MPH; Adrienne Cupples, PhD

Background and Purpose—The rate of stroke among warfarin-treated patients in SPORTIF V was approximately half that of patients enrolled in SPORTIF III (1.16%/year versus 2.30%/year). SPORTIF III was an open-label trial comparing ximelagatran with warfarin for stroke prevention in atrial fibrillation. SPORTIF V was a double-blind trial performed in North America. The trial design was otherwise identical. We sought to determine if differences in baseline characteristics, use of potentially risk-modifying medications, or anticoagulation control help to explain the lower risk of stroke among warfarin-treated patients in SPORTIF V.

Methods—Cox regression with stepwise model selection was used to define the covariates independently associated with stroke. Secondary analyses identified covariates with the strongest influence on the study factor (V/III). These covariates were then added to the primary model. Cox regression was used to determine the degree of confounding exerted by these covariates that might help to explain the differences between the trials.

Results—Independent risk factors for stroke on warfarin included prior stroke/transient ischemic attack, coronary artery disease, international normalized ratio, weight, and study. Patients in SPORTIF V were at half the risk as those in SPORTIF III. We found that lower international normalized ratio variability, a higher proportion of prevalent warfarin use, lower systolic blood pressure, high-density lipoprotein, and a greater proportion of statin use among patients in SPORTIF V collectively conferred a lower risk of stroke.

Conclusion—Differences in blood pressure control, international normalized ratio variability, proportion of prevalent warfarin users, statin exposure, and high-density lipoprotein collectively conferred a lower risk of stroke to patients in SPORTIF V. These findings suggest that the different event rates were not due to chance and provide potential insights into stroke risk among warfarin-treated patients with atrial fibrillation. (Stroke. 2008;39:3009-3014.)

Key Words: atrial fibrillation ■ stroke ■ warfarin

Vitamin K antagonists (eg, warfarin) have been the mainstay of oral anticoagulation for stroke prevention in atrial fibrillation (AF). It is widely recognized that newer antithrombotic agents are needed because of warfarin’s narrow therapeutic index and its interaction with food and other drugs. The variability in the dose–response of warfarin mandates frequent monitoring, which also imposes a significant barrier to its use. The first of these newer agents, an oral direct thrombin inhibitor, ximelagatran, was evaluated in 2 clinical trials enrolling an unprecedented 7329 patients (Stroke Prevention using an ORal Thrombin Inhibitor in atrial Fibrillation [SPORTIF]). SPORTIF III was an open-label trial comparing ximelagatran with warfarin conducted in Europe, Asia, Australia, and New Zealand; SPORTIF V was a double-blind trial performed in North America. The trial design was otherwise identical. The primary end point in both trials was all strokes, both ischemic and hemorrhagic, and systemic embolic events. Although potential risk factors were well balanced across treatment arms within each trial, there were significant differences across trials between SPORTIF III and SPORTIF V. The stroke rate among warfarin-treated patients in the North American trial was approximately half that of patients enrolled in SPORTIF III (1.16%/year versus 2.30%/year) despite similar adherence and anticoagulation control.

The objective of our study was to formally assess this difference in event rates among warfarin-treated patients to determine if differences in baseline characteristics, use of potentially risk-modifying concomitant therapies, or variability in control of anticoagulation might help to explain the seemingly lower risk of warfarin-treated patients enrolled in SPORTIF V. Understanding these differences would facili-
tate a more informed interpretation of the 2 trials, provide potential insights into stroke risk among warfarin-treated patients with AF, and highlight important considerations for randomized trials in AF with warfarin as the comparator.

Materials and Methods

The design, patient demographics, and main results of the 2 trials have previously been published. The primary end point for both trials included ischemic stroke, hemorrhagic stroke, and systemic embolic events. SPORTIF III enrolled 1703 patients in the warfarin arm. Median follow-up was 17.9 months. In SPORTIF V, 1962 patients were randomized to warfarin and the median follow-up was 20.1 months. In total, 93 primary events (9 primary intracerebral hemorrhages) were confirmed among patients randomized to warfa-rin in the 2 trials. Outcome assessment was blinded to treatment in both trials.

Variables

Anticoagulation Control (time-in-range, international normalized ratio variability, prevalent warfarin use) Warfarin dosing and monitoring of the international normalized ratio (INR) were different in the 2 trials. SPORTIF V used a double-blind design with sham INR testing. A standardized point-of-care instrument and uniform thromboplastin reagent were used for the majority of INR measurements. Warfarin dosing was performed by a central laboratory. In the open-label SPORTIF III trial that involved 23 countries, warfarin management was conducted locally by investigators or individual patient physicians. Assays encompassed a variety of methods, reagents, and instruments.

Anticoagulation control within the 2 trials was determined by time-in-range analyses using linear interpolation between INR measurements. Per protocol, INR measurements were mandated at least every 31 days. As a result, gaps in monitoring were rare. Variability in INR was assessed using SD. An additional variable of interest was the proportion of patients taking warfarin at study entry. To the extent that prevalent users represent a warfarin-tolerant population, this survivor bias would be reflected in fewer events overall, both ischemic and hemorrhagic, lower INR variability, and a higher percentage of time in range. The increased INR variability attributable to new warfarin use would heighten the already expected differences due to the use of multiple thromboplastin reagents, instruments, and testing methodologies. Differences in INR variability or time in the therapeutic range may have placed SPORTIF V patients at lower risk for the primary end point.

Potential Risk-Modifying Concomitant Therapy Differences in exposure to other medications that have the potential to alter stroke risk over time were also evaluated. Ascertainment of concomitant medications in the SPORTIF program was conducted at prespecified points throughout the trial periods. Specific drugs of interest included hydroxymethylglutaryl coenzyme A reductase inhibitors (statins), aspirin, and drugs that inhibit the renin–angioten-sin–aldosterone system. Because the majority of patients who were taking these medications at baseline were still taking them at the end of follow-up, we analyzed medication as a binary variable.

Additional Covariates Other variables of interest that may have contributed to differences in risk included demographic features, known risk factors for stroke (hypertension, heart failure, diabetes, and prior stroke), weight, body mass index, high-density lipoprotein (HDL), low-density lipoprotein, creatinine clearance, and smoking status. Because differences in blood pressure control may have existed between the 2 trials, we also assessed the effect of mean systolic and diastolic blood pressure in addition to analyzing hypertension as a binary variable. Physical examinations that included determination of vital signs were performed at prespecified intervals according to the study protocol:

baseline, 1, 3, and 6 months and 6-month intervals throughout the trial period.

Statistical Analyses

The Kolmogorov-Smirnov test was adopted for testing the equality of different empirical distribution functions. Cox regression models with stroke/systemic embolic event as the dependent variable were used to first define the univariate associations of the covariates and outcome among patients taking warfarin in both trials. Stepwise model selection was used for the multivariable Cox regression to define the covariates that were independently associated with stroke and included only those variables from univariate analysis that achieved significance at the 5% level and maintained this level of significance in the presence of other selected covariates in the multivariate model. In the primary univariate analyses, a statistically significant study factor (V/III) was found, ie, patients on warfarin in SPORTIF V were at approximately half the estimated risk for stroke as patients on warfarin in SPORTIF III (hazard ratio=0.541; 95% CI, 0.358 to 0.824). We next sought to define the relationship between covariates and the study factor with bivariate analyses. Using Cox regression, we evaluated whether differences in distributions of risk factors or other variables between the 2 studies could help to explain the difference in event rates. Models with study factor (V/III) plus one additional covariate, one at a time, were used to assess the effect of the covariate on the estimated hazard ratio (0.54) of the study factor. Those factors having the largest impact were then added to the primary multivariable model. Analyses were performed in SAS (version 8.2; SAS Institute, Inc, Cary, NC).

Results

Baseline Characteristics

As previously highlighted in the pooled analysis, there were significant differences in baseline characteristics between SPORTIF V and SPORTIF III. Patients randomized to warfarin in the North American (SPORTIF V) trial were older (mean age, 71.6 years versus 70.1 years) and more had hypertension (Table 1). Fewer patients had a history of stroke (18% versus 24%), and a greater proportion of patients were obese. In SPORTIF V, more patients were taking warfarin at study entry (85% versus 73%), a statin (47% versus 30%), and aspirin (25% versus 17%). Similar proportions of patients were taking angiotensin-converting enzyme inhibitors.

Blood Pressure Control

Although more patients in SPORTIF V had hypertension, blood pressure was controlled to a greater degree in SPORTIF V (Table 2). Mean systolic blood pressure at entry was 132.6 mm Hg versus 139.0 mm Hg among patients in SPORTIF III. Longitudinal assessment of blood pressure revealed that 78% of warfarin-treated patients in SPORTIF V had a mean systolic blood pressure of less than 140 mm Hg compared with 63% of warfarin-treated patients in SPORTIF III (P<0.001).

Anticoagulation Control

Despite different methodologies for warfarin dosing and INR measurement, the overall time spent in the therapeutic range, 2.0 to 3.0, was nearly identical in the 2 trials, 68% versus 66% for SPORTIF V versus SPORTIF III and 83% versus 81% for time in the expanded range of 1.8 to 3.2 as has been previously reported. Proportion of time in the INR range <2 was 20% versus 19% and 12% versus 15% for INR >3.
However, the proportion of individual patients whose INR was maintained between 2.0 and 3.0 for at least 50% of the time was different in SPORTIF V versus SPORTIF III, 85% versus 79.5% (P < 0.001). This finding at least in part reflects the higher proportion of prevalent warfarin users enrolled in the North American trial (Figures 1 and 2). INR variability was lower in SPORTIF V (SD, 0.63 versus 0.72). INR variability was considerably lower among those patients taking warfarin at study entry compared with those newly starting therapy (SD, 0.61 versus 0.85; P < 0.001).

### Table 1. Baseline Clinical Characteristics of Warfarin-Treated Patients in SPORTIF III versus SPORTIF V

<table>
<thead>
<tr>
<th>Variables, % (n)</th>
<th>SPORTIF III (N = 1703)</th>
<th>SPORTIF V (N = 1962)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥75 y</td>
<td>33 (565)</td>
<td>42 (820)†</td>
</tr>
<tr>
<td>Female</td>
<td>30 (507)</td>
<td>31 (609)</td>
</tr>
<tr>
<td>Prior stroke/TIA</td>
<td>24 (405)</td>
<td>18 (348)†</td>
</tr>
<tr>
<td>Hypertension</td>
<td>72 (1230)</td>
<td>81 (1582)†</td>
</tr>
<tr>
<td>Heart failure‡</td>
<td>34 (584)</td>
<td>40 (788)†</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>22 (377)</td>
<td>25 (483)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>40 (675)</td>
<td>48 (944)†</td>
</tr>
<tr>
<td>Creatinine clearance &lt;50, mL/min</td>
<td>14 (228)</td>
<td>13 (260)</td>
</tr>
<tr>
<td>Vitamin K antagonist at entry</td>
<td>73 (1235)</td>
<td>85 (1661)†</td>
</tr>
<tr>
<td>Body weight &gt;100 kg</td>
<td>11 (182)</td>
<td>25 (494)†</td>
</tr>
<tr>
<td>Body mass index &gt;30, kg/m²</td>
<td>31 (520)</td>
<td>40 (790)†</td>
</tr>
<tr>
<td>HDL, mmol/L, mean (SD)§</td>
<td>1.27 (0.38)</td>
<td>1.20 (0.39)†</td>
</tr>
<tr>
<td>LDL, mmol/L, mean (SD)§</td>
<td>3.16 (0.93)</td>
<td>2.82 (0.86)†</td>
</tr>
<tr>
<td>Concomitant medications, % (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>17 (290)</td>
<td>25 (482)†</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitor</td>
<td>53 (896)</td>
<td>53 (1041)</td>
</tr>
<tr>
<td>Angiotensin-receptor blocker</td>
<td>12 (202)</td>
<td>15 (296)</td>
</tr>
<tr>
<td>HMG-CoA reductase inhibitor</td>
<td>30 (504)</td>
<td>47 (928)†</td>
</tr>
<tr>
<td>ACEI + HMG-CoA reductase inhibitor</td>
<td>17 (290)</td>
<td>29 (566)†</td>
</tr>
</tbody>
</table>

*Stroke Prevention using an ORal Thrombin Inhibitor in atrial Fibrillation = SPORTIF.
†P < 0.001.
‡Left ventricular ejection fraction <40% or symptomatic heart failure.
§Multiply by 39 to convert to mg/dL.
TIA indicates transient ischemic attack; LDL, low-density lipoprotein; HMG-CoA, hydroxymethylglutaryl coenzyme A; ACEI, angiotensin-converting enzyme inhibitor.

However, the proportion of individual patients whose INR was maintained between 2.0 and 3.0 for at least 50% of the time was different in SPORTIF V versus SPORTIF III, 85% versus 79.5% (P < 0.001). This finding at least in part reflects the higher proportion of prevalent warfarin users enrolled in the North American trial (Figures 1 and 2). INR variability was lower in SPORTIF V (SD, 0.63 versus 0.72). INR variability was considerably lower among those patients taking warfarin at study entry compared with those newly starting therapy (SD, 0.61 versus 0.85; P < 0.001).

### Table 2. Distribution of Warfarin-Treated Patients in SPORTIF III and SPORTIF V by Mean Systolic Blood Pressure During the Trial Period (P < 0.001)

<table>
<thead>
<tr>
<th>Mean SBP Category, mm Hg</th>
<th>SPORTIF III (N = 1703)</th>
<th>SPORTIF V (N = 1962)</th>
</tr>
</thead>
<tbody>
<tr>
<td>84–119.9</td>
<td>214 (12.6%)</td>
<td>410 (20.9%)</td>
</tr>
<tr>
<td>120–139.9</td>
<td>865 (50.8%)</td>
<td>1111 (56.6%)</td>
</tr>
<tr>
<td>140–159.9</td>
<td>561 (32.9%)</td>
<td>411 (21.0%)</td>
</tr>
<tr>
<td>160–179.9</td>
<td>61 (3.6%)</td>
<td>30 (1.5%)</td>
</tr>
<tr>
<td>180–191.7</td>
<td>2 (0.1%)</td>
<td>0</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure.

### Figure 1. Distribution of patients on warfarin by percentage of time spent in the INR range of 2 to 3. The hypothesis of equal distributions was rejected, P = 0.0004, by the Kolmogorov-Smirnov test.

### Figure 2. Distributions for the percentage of time by INR level according to warfarin status at entry. The hypothesis of equal distributions was rejected, P < 0.0001, by the Kolmogorov-Smirnov test.

### Risk Factors for Stroke and Study Factor Analysis

Among patients taking warfarin, independent risk factors for stroke included prior stroke/transient ischemic attack, coronary artery disease, time in INR range, weight, and study, ie, patients in SPORTIF V were at approximately 40% lower risk than patients in SPORTIF III (Table 3). Covariates identified in bivariate analyses as having the strongest influence on the study factor (V/III) were added to the primary multivariable model. As shown in Table 4, after adjusting for these 5 factors, ie, systolic blood pressure, HDL, statin use, INR variability, and prevalent warfarin use, the effect of the study factor was diminished and no longer statistically significant. This finding suggests that the collective impact (joint confounding) of these covariates helps to explain the disparate stroke event rates experienced within the 2 trials. These factors were sufficiently correlated with the study factor such that after adjusting for them, there was no longer a significant difference between the study groups.

### Discussion

Warfarin is highly effective in reducing the risk of ischemic stroke in AF. In the pooled analysis of the first 5 randomized trials, the event rate on placebo was 4.94% compared with 1.91% on oral anticoagulant therapy. In the open-label SPORTIF III trial, the rate of all stroke/systemic embolism was 2.30% on warfarin and 1.16% in SPORTIF V. The difference in event rates on warfarin between the 2 trials has not previously been studied in detail. In this analysis, we found a joint confounding effect of systolic blood pressure,
HDLC, statin use, INR variability, and prevalent warfarin status that may help to explain the lower event rate among patients taking warfarin in SPORTIF V.

Despite similar aggregate time in range, more individual patients in SPORTIF V maintained the therapeutic range compared with SPORTIF III. SPORTIF V enrolled 85% of patients taking warfarin at study entry compared with 73% in SPORTIF III, and INR variability was less. SPORTIF V used a double-blind design with sham INR testing, a standardized point-of-care instrument, uniform thromboplastin, and a centralized laboratory for dosing of warfarin. These controlled experimental conditions would be difficult to duplicate in real-world care, and in this respect, SPORTIF III more closely reflects clinical practice. The effect of INR intensity on risk of stroke has been well described.9,10 This was also recently shown in a pooled analysis of warfarin-treated patients in the SPORTIF program.11 White et al found the rate of stroke/systemic embolism to be 2.10% among patients with <60% time in the therapeutic INR range compared with 1.07% for patients with >75% time in range. In contrast to the early AF trials that established the efficacy of warfarin versus placebo, newer antithrombotic drugs are being compared with warfarin. There is an important survivor bias inherent to prevalent warfarin use that has been underrecognized. New use of warfarin is more closely associated with incident AF, which is a risk-prone period for stroke and hemorrhage.12–15 Prevalent warfarin use denotes a warfarin-tolerant, lower-risk population.16 In addition, patients who have been taking warfarin for longer periods of time have a unique training advantage in knowing their own individual triggers for aberrant INR control and have benefited from multiple medical encounters that reinforced healthy behaviors and medication adherence. This frequent interface with medical care may also have helped to optimize other stroke risk factors through improved control of hypertension, diabetes, and heart failure. For all of these reasons, the distinction between warfarin-naive and prevalent warfarin use is important for trials with warfarin as the comparator. Event rates will be influenced by the proportions of these patients enrolled.

Hypertension is a potent risk factor for stroke and its effects persist despite anticoagulant therapy.9,17 In a pooled analysis of SPORTIF data, Lip et al found the rate of stroke/systemic embolism to increase substantially at mean systolic blood pressures of 140 mm Hg and greater (2.4% versus 1.4% for mean systolic blood pressure <140 mm Hg).16 In addition to the differences related to warfarin, our data suggest that blood pressure control, statin use, and HDL collectively lowered the risk of patients with prior stroke/TIA versus placebo, newer antithrombotic drugs are being compared with warfarin. There is an important survivor bias inherent to prevalent warfarin use that has been underrecognized. New use of warfarin is more closely associated with incident AF, which is a risk-prone period for stroke and hemorrhage.12–15 Prevalent warfarin use denotes a warfarin-tolerant, lower-risk population.16 In addition, patients who have been taking warfarin for longer periods of time have a unique training advantage in knowing their own individual triggers for aberrant INR control and have benefited from multiple medical encounters that reinforced healthy behaviors and medication adherence. This frequent interface with medical care may also have helped to optimize other stroke risk factors through improved control of hypertension, diabetes, and heart failure. For all of these reasons, the distinction between warfarin-naive and prevalent warfarin use is important for trials with warfarin as the comparator. Event rates will be influenced by the proportions of these patients enrolled.

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Distinct from stroke risk factors derived from placebo populations, risk of stroke among individuals taking warfarin provides insight into factors that either influence risk independent of anticoagulation or factors that modulate the efficacy of warfarin. There are comparatively fewer studies of stroke risk among warfarin-treated patients with AF. The prospective study of 364 individuals by Poli and colleagues
was limited by the small number of events (n=21).\textsuperscript{17} We found prior stroke to persist as a strong risk factor among warfarin-treated patients as previously reported.\textsuperscript{9,17} Coronary artery disease has not consistently been found to be an independent risk factor for stroke in AF after adjusting for other known vascular risk factors.\textsuperscript{8,32} However, coronary artery disease is a marker of atherosclerotic burden and an independent predictor of complex aortic plaque, which has been shown to be independently associated with high thromboembolic risk among patients with AF.\textsuperscript{33} The protective effect of weight is unexpected. The paradoxical effect of obesity on cardiovascular outcomes has been reported in patients with hypertension and coronary artery disease, patients with heart failure, and in patients treated with early percutaneous coronary intervention for unstable angina/non-ST-segment elevation myocardial infarction.\textsuperscript{34–36} Touted mechanisms include detection and treatment bias among obese patients compared with nonobese patients, upregulation of endogenous cannabinoids, and complex effects of inflammatory cytokines and adiponectin.\textsuperscript{37–40} Weight may also reflect warfarin dose and warfarin sensitivity as suggested by the pooled analysis that found improved INR control with increasing weight.\textsuperscript{11}

Our study has several limitations. The findings were derived from a post hoc analysis of the SPORTIF trials. Residual unmeasured confounding may still exist. We were unable to measure the effect of homocysteine, which has been reported to be a risk factor for stroke among patients with AF taking oral anticoagulants.\textsuperscript{17} Given the use of multiple thromboplastins of varying sensitivity, comparison of INR distributions across trials is less than optimal. The most valid comparison would require reassay of plasma at a reference laboratory.

Summary
In this study, we sought to better understand the differences in event rates among warfarin-treated patients with AF enrolled in 2 contemporaneous trials. We found that differences in blood pressure control, INR variability, proportion of prevalent warfarin users, statin exposure, and HDL collectively conferred a lower risk of stroke to patients in SPORTIF V. These findings suggest that the different event rates were not due to chance and provide potential insights into stroke risk among warfarin-treated patients with AF.

Source of Funding
AstraZeneca funded this study and the SPORTIF III and SPORTIF V trials.

Disclosures
E.M.H. has served in an advisory capacity and received research grant support from AstraZeneca and Bristol-Myers Squibb; L.F. is an employee of AstraZeneca.

References


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*Stroke*. 2008;39:3009-3014; originally published online August 14, 2008; doi: 10.1161/STROKEAHA.108.514935

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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