Secondary Stroke Prevention With Ximelagatran Versus Warfarin in Patients With Atrial Fibrillation
Pooled Analysis of SPORTIF III and V Clinical Trials

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Background and Purpose—Patients with nonvalvular atrial fibrillation and prior stroke or transient ischemic attack (TIA) are at high risk for recurrent stroke. We investigated whether ximelagatran was noninferior to warfarin in patients with prior stroke or TIA.

Methods—We analyzed pooled data from the SPORTIF III and V trials in patients with prior stroke/TIA. The primary outcome was the composite annual rate of both ischemic and hemorrhagic strokes and systemic embolic events. Secondary analyses considered ischemic and hemorrhagic strokes separately, bleeding, and nonrandomized, concomitant therapy with aspirin ≤ 100 mg/d.

Results—Patients from SPORTIF III (n = 3407) and SPORTIF V (n = 3922) trials were categorized by prior stroke/TIA (21%) versus no prior stroke/TIA (79%) and by treatment group (ximelagatran vs warfarin). The primary event rate in patients with prior stroke/TIA was 2.83%/y with ximelagatran and 3.27%/y with warfarin (absolute difference, −0.44%; 95% CI, −1.88 to 1.01; P = 0.625). In those without prior stroke/TIA, the primary event rate was 1.31%/y with ximelagatran and 1.26%/y with warfarin (P = NS). Ischemic strokes outnumbered cerebral hemorrhages with both warfarin (31 of 36) and ximelagatran (30 of 32) treatment (difference between treatments was not significant). Combining aspirin with either anticoagulant was associated with higher rates of major bleeding (1.5%/y with warfarin and 4.95%/y with warfarin plus aspirin, P = 0.004; 2.35%/y with ximelagatran and 5.09%/y with ximelagatran plus aspirin, P = 0.046) but not lower rates of primary events.

Conclusions—Ximelagatran was at least as effective as well-controlled warfarin for the secondary prevention of stroke. The nonrandomized, concomitant treatment with aspirin and anticoagulation was associated with increased bleeding without evidence of a reduction in primary outcome events. (Stroke. 2007;38:874-880.)

Key Words: atrial fibrillation • aspirin • direct thrombin inhibitor • stroke prevention • warfarin
Clearance is predominantly by the kidneys. In the SPORTIF trials, liver enzyme elevations (3 times the upper limit of normal) occurred in 6% of patients.

In this prespecified substudy of the SPORTIF III and V trials, we compared the effects of ximelagatran and warfarin in patients with prior stroke/TIA (secondary stroke prevention). Other SPORTIF publications have presented the primary results of the individual trials (SPORTIF III and V),\(^{12,14}\) a pooled analysis for the combined patient group treated (n = 7329),\(^{15}\) and a cost-effectiveness study.\(^{16}\) We selected the stroke/TIA subgroup because it has the highest risk for stroke recurrence yet may also be more susceptible to adverse effects. We contrasted the outcomes of patients with prior stroke/TIA with those of patients who did not have a stroke/TIA history. We also investigated whether the combination of aspirin with anticoagulation therapy appears to offers benefits for secondary stroke prevention compared with anticoagulation alone.

**Subjects and Methods**

**Patients**

SPORTIF III was conducted at 259 centers in 23 countries in Europe, Asia, and Australasia with randomization of 3407 patients between August 2000 and September 2001. SPORTIF V was conducted at 409 centers in the United States and Canada with randomization of 3922 patients between July 2000 and December 2001. The rationale and design of SPORTIF III and V have been previously described.\(^{13}\) Informed consent was required for enrollment, and local ethics committees approved the research protocol. An Executive Steering Committee oversaw the design and implementation of each study. An independent safety monitoring board independently evaluated study conduct and patient safety, and a Central Event Adjudication Committee reviewed all pertinent medical records, including laboratory and imaging data, and evaluated all deaths.

**Inclusion and Exclusion Criteria**

Patients eligible for participation in SPORTIF III and V required ECG documentation on 2 occasions of AF within 2 weeks of randomization and 1 or more additional stroke risk factor, including hypertension; age 75 years or older; prior stroke/TIA/systemic embolus; left ventricular dysfunction, or heart failure. Stroke was defined as the abrupt onset over minutes to hours of a focal neurological deficit that persisted for >24 hours and was caused by altered cerebral circulation in the territory of a cervical or cerebral vessel. Imaging was required to exclude other diagnostic concerns (eg, masses) and to distinguish cerebral hemorrhage from cerebral ischemia before enrollment. If the focal neurological deficit lasted <24 hours and completely resolved, it was classified as a TIA.

Principal exclusion criteria for enrollment included mitral stenosis or atrial fibrillation; age 75 years or older; prior stroke/TIA/systemic emboli; left ventricular dysfunction, or heart failure. Stroke was defined as the abrupt onset over minutes to hours of a focal neurological deficit that persisted for >24 hours and was caused by altered cerebral circulation in the territory of a cervical or cerebral vessel. Imaging was required to exclude other diagnostic concerns (eg, masses) and to distinguish cerebral hemorrhage from cerebral ischemia before enrollment. If the focal neurological deficit lasted <24 hours and completely resolved, it was classified as a TIA.

Principal exclusion criteria for enrollment included mitral stenosis or atrial fibrillation; age 75 years or older; prior stroke/TIA/systemic emboli; left ventricular dysfunction, or heart failure. Stroke was defined as the abrupt onset over minutes to hours of a focal neurological deficit that persisted for >24 hours and was caused by altered cerebral circulation in the territory of a cervical or cerebral vessel. Imaging was required to exclude other diagnostic concerns (eg, masses) and to distinguish cerebral hemorrhage from cerebral ischemia before enrollment. If the focal neurological deficit lasted <24 hours and completely resolved, it was classified as a TIA.

**Outcomes**

**Primary Outcome**

The primary outcome measure was a composite of ischemic stroke, hemorrhagic stroke, and SEEs. The annual event rates for the primary outcome comparing warfarin treatment with ximelagatran treatment in patients with or without prior

**Outcome Measures**

The primary outcome for this substudy was the rate of primary events, which were defined as the composite of all strokes (ischemic and hemorrhagic) and systemic embolic events (SEEs) in patients with a prior history of stroke/TIA, based on treatment allocation to either warfarin or ximelagatran. Secondary end points included the proportion of cerebral hemorrhage to total stroke, the rate of major bleeding, and the association between concomitant low-dose aspirin use and primary outcome events or major bleeding.

**Statistical Analysis**

The primary analysis compared warfarin and ximelagatran for the secondary prevention of stroke (ischemic or hemorrhagic) or systemic emboli according to the intention to treat. The objective was to establish whether ximelagatran was noninferior to dose-adjusted warfarin within a prespecified absolute margin (Δ) of 2.0%/y for the 1-sided 97.5% CI around the difference in rates of primary events. All patients were followed up for occurrences of primary events and mortality until study closure, so all remaining end points were recorded for the total duration of the study period. The end points of ischemic and hemorrhagic stroke and SEEs were analyzed according to the intention to treat. Major systemic bleeding end points were analyzed by an on-treatment approach.\(^{12,14}\) Fisher’s exact test was used to compare groups with a 2-tailed approach and 95% CIs. Multivariate analyses were performed to derive potential prognostic factors with 16 variables in patients with prior stroke or TIA in a stepwise model. All the analyses were performed with SAS (version 8.2; SAS Institute, Inc, Cary, NC). More detailed descriptions of the statistical analyses used in the SPORTIF III and V trials have been published previously.\(^{13}\)

**Results**

**Patient Characteristics**

Patients with prior stroke/TIA constituted 24% of the SPORTIF III study subjects, 18% of the SPORTIF V population, and 21% of the combined SPORTIF III and V study subjects (Table 1). For the combined SPORTIF III and V group, 21.0% of the patients had a prior stroke and/or TIA, 12.5% had a prior stroke, 8.5% had a prior TIA only, and 2.1% had both. We dichotomized this pooled group into no prior stroke/TIA and prior stroke/TIA, based on the planned prespecified subgroup analysis. Compared with patients without prior stroke/TIA, patients with prior thromboembolism were more likely to be Oriental, older than 75 years, have 3 or more risk factors for stroke besides AF, and have a preexisting disability as measured by the modified Rankin Scale. Demographic features were balanced between the treatment groups with warfarin or ximelagatran (Table 1). For the warfarin treatment groups, the mean INR was 2.42 (SD = 0.67) and time in the INR range of 2 to 3 was 66.8% for patients with prior stroke/TIA; the INR was 2.45 (SD = 0.67) and time in the INR range of 2 to 3 was 67.8% for those without a prior stroke/TIA. For SPORTIF III, patients were followed up for a mean duration of 17.4 months. For SPORTIF V, patients were followed up for a mean duration of 20 months.

**Primary Outcome**

The primary outcome measure was a composite of ischemic stroke, hemorrhagic stroke, and SEEs. The annual event rates for the primary outcome comparing warfarin treatment with ximelagatran treatment in patients with or without prior

**Highlights**

- Ximelagatran was noninferior to dose-adjusted warfarin for secondary stroke prevention in patients with prior stroke/TIA.
- Major systemic bleeding end points were analyzed by an on-treatment approach.
- Multivariate analyses were performed to derive potential prognostic factors with 16 variables in patients with prior stroke or TIA in a stepwise model.
- More detailed descriptions of the statistical analyses used in the SPORTIF III and V trials have been published previously.

**Acknowledgment**

This research was supported by a grant from Bayer CropScience, Shawnee Mission, Kansas. The authors thank our core study group investigators and the patients and families who participated in the SPORTIF trials.
TABLE 1. Demographic and Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Ximelagatran</th>
<th>Warfarin</th>
<th>Prior Stroke/TIA</th>
<th>No Prior Stroke/TIA</th>
<th>P</th>
<th>Prior Stroke/TIA</th>
<th>No Prior Stroke/TIA</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>n=786</td>
<td>n=2878</td>
<td>533 (68%)</td>
<td>1990 (69%)</td>
<td>0.487</td>
<td>515 (68%)</td>
<td>2034 (70%)</td>
<td>0.450</td>
</tr>
<tr>
<td>Hypertension</td>
<td>577 (73%)</td>
<td>2236 (78%)</td>
<td>0.013</td>
<td></td>
<td></td>
<td>565 (75%)</td>
<td>2247 (77%)</td>
<td>0.227</td>
</tr>
<tr>
<td>Age ≥75 y</td>
<td>348 (44%)</td>
<td>1071 (37%)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td>330 (44%)</td>
<td>1055 (36%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No. of risk factors &gt;3</td>
<td>289 (37%)</td>
<td>315 (11%)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td>282 (37%)</td>
<td>315 (11%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous smoker</td>
<td>363 (46%)</td>
<td>1402 (49%)</td>
<td>0.212</td>
<td></td>
<td></td>
<td>371 (49%)</td>
<td>1414 (49%)</td>
<td>0.744</td>
</tr>
<tr>
<td>LVD</td>
<td>226 (29%)</td>
<td>1083 (38%)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td>247 (33%)</td>
<td>1125 (39%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Concurrent aspirin use</td>
<td>152 (20%)</td>
<td>540 (19%)</td>
<td>0.442</td>
<td></td>
<td></td>
<td>186 (25%)</td>
<td>540 (19%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DM</td>
<td>195 (25%)</td>
<td>670 (23%)</td>
<td>0.368</td>
<td></td>
<td></td>
<td>180 (24%)</td>
<td>680 (23%)</td>
<td>0.772</td>
</tr>
<tr>
<td>CAD</td>
<td>340 (43%)</td>
<td>1320 (46%)</td>
<td>0.196</td>
<td></td>
<td></td>
<td>332 (44%)</td>
<td>1287 (44%)</td>
<td>0.967</td>
</tr>
<tr>
<td>Modified Rankin score ≥1</td>
<td>366 (47%)</td>
<td>481 (17%)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td>323 (43%)</td>
<td>543 (19%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>682 (87%)</td>
<td>2687 (93%)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td>658 (87%)</td>
<td>2730 (94%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Black</td>
<td>16 (2%)</td>
<td>51 (2%)</td>
<td>0.652</td>
<td></td>
<td></td>
<td>14 (2%)</td>
<td>47 (2%)</td>
<td>0.632</td>
</tr>
<tr>
<td>Oriental</td>
<td>83 (11%)</td>
<td>133 (5%)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td>79 (10%)</td>
<td>127 (4%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

LVD indicates left ventricular dysfunction; DM, diabetes mellitus; and CAD, coronary artery disease.

TABLE 2. Efficacy of Ximelagatran vs Warfarin in Preventing Stroke/SEE in Patients With/Without Prior Stroke/TIA (ITT Population)*

<table>
<thead>
<tr>
<th></th>
<th>Prior Stroke/TIA</th>
<th>No Prior Stroke/TIA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ximelagatran</td>
<td>Warfarin</td>
</tr>
<tr>
<td>Events*</td>
<td>33 36</td>
<td>58 57</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>2 5</td>
<td>4 6</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>30 31</td>
<td>47 51</td>
</tr>
<tr>
<td>SEE</td>
<td>1 1</td>
<td>9 2</td>
</tr>
<tr>
<td>Patient-years</td>
<td>1164 1101</td>
<td>4442 4526</td>
</tr>
<tr>
<td>Event rate, %/y</td>
<td>2.83 3.27</td>
<td>1.31 1.26</td>
</tr>
<tr>
<td>95% CI</td>
<td>1.87–2.80</td>
<td>2.20–4.34</td>
</tr>
<tr>
<td>P</td>
<td>0.625</td>
<td>0.852</td>
</tr>
</tbody>
</table>

*As per the Central Event Adjudication Committee.

Combined treatment data (warfarin and ximelagatran). For the 1539 patients composing the secondary prevention population, 395 (26%) had a prior stroke/TIA within 1 year of enrollment, and primary event rates were 4.3%/y for the pooled group; 626 patients were enrolled between 1 and 5 years of prior stroke/TIA and the primary event rate was 3.0%/y; 518 patients were enrolled 5 years or longer after prior stroke/TIA and the primary event rate was 2.2%/y. For patients enrolled within 1 year of prior stroke/TIA, primary event rates were comparable for ximelagatran (4.1%/y) and warfarin (4.5%/y).

The primary outcome measure was largely dominated by ischemic strokes, because hemorrhagic strokes and SEEs occurred infrequently. In the entire SPORTIF population (primary and secondary prevention combined), hemorrhagic stroke accounted for 9.7% of all strokes (11.8% for warfarin-treated patients and 7.2% for ximelagatran-treated patients; P=0.322). In patients with prior stroke/TIA, hemorrhagic stroke accounted for 13.8% of all strokes in the warfarin-treated group and 6.3% in the ximelagatran-treated group (P=0.434). In patients without prior stroke/TIA, hemorrhagic stroke constituted 10.5% of all strokes in the warfarin-treated group and 7.8% in the ximelagatran-treated group (P=0.746).

The univariate hazard ratio (HR) for recurrent thromboembolism was increased among patients ≥75 years (HR, 1.67; 95% CI, 1.03 to 2.68; P=0.0354) and by study (SPORTIF III versus V: HR, 2.49; 95% CI, 1.46 to 4.24; P=0.0008). When treatment with ximelagatran was compared with warfarin, no statistically significant interaction was identified. In the analysis of the results from the full study population, there was a significant interaction (P=0.026) between study and study treatment. This was not apparent among secondary prevention patients (P=0.31 for the interaction). The elevated HR between SPORTIF III and V is related to the higher event rates in SPORTIF III compared with SPORTIF V, but further

stroke/TIA are shown in Table 2. For patients with a history of stroke/TIA, there was a trend toward a lower primary event rate with ximelagatran. The absolute difference in the annual primary event rate was −0.44% (95% CI, −1.88 to 1.01). Therefore, because the upper limit of the 95% CI was <2, noninferiority was confirmed. The primary analysis was reinforced by a sensitivity analysis based on a on-treatment approach, resulting in an estimated difference of −1.00% (95% CI, −2.49 to 0.48), numerically favoring ximelagatran.

When the 2 treatment groups were combined, event rates for the primary outcome measure in patients with prior stroke/TIA were more than double those in the primary prevention population (3.05% versus 1.28%; P=0.001). These event rates remained divergent throughout the course of the study (Figure 1).

We looked at primary event rates based on how recent the prior stroke/TIA occurred before enrollment in the trial by using

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analysis does not suggest that this was related to the effects of anticoagulation treatment for secondary prevention.

Secondary Outcomes

Effect of Aspirin

Twenty percent of patients with prior stroke/TIA assigned to ximelagatran and 25% of patients with prior stroke/TIA assigned to warfarin received concomitant treatment with low-dose aspirin (100 mg/d or less) on the advice of their physicians (Table 1). When combined aspirin and anticoagulant therapy was used by patients with prior stroke/TIA (Tables 3 and 4), the univariate HRs for recurrent thromboembolism were increased, though not significantly (ximelagatran HR, 1.51; 95% CI, 0.73 to 3.11; warfarin HR, 1.51; 95% CI, 0.77 to 2.99). The HR for combination therapy (either ximelagatran or warfarin plus aspirin) also remained increased when a multivariate model was used to adjust for other potential prognostic factors (HR, 1.62; 95% CI, 0.99 to 2.67; *P*=0.0568; Table 4). Adding aspirin to either ximelagatran or warfarin was not associated with an increase in cerebral hemorrhage rates (no cerebral hemorrhages occurred in patients on aspirin plus warfarin therapy; 1 occurred in a patient treated with aspirin plus ximelagatran).

Major Bleeding

There was a trend toward slightly higher bleeding in patients with prior stroke/TIA compared with patients without prior stroke/TIA (2.70% versus 2.05%; *P*=0.086). In patients with prior stroke/TIA, there was no significant difference in major bleeding rates between ximelagatran and warfarin with or without aspirin cotreatment (Figure 2). Cerebral hemorrhage rates in patients with prior stroke/TIA were 0.17%/y with ximelagatran compared with 0.45%/y for warfarin (*P* = 0.277). For patients without prior stroke/TIA, the respective rates were 0.09%/y and 0.13%/y (*P*=0.754).

Concomitant aspirin+anticoagulant therapy was associated with a significant increase in major bleeding compared with anticoagulant therapy alone. The increased risk of major bleeding associated with combination therapy was greater with warfarin (3.3-fold) than with ximelagatran (2.2-fold). For example, major bleeding increased with warfarin therapy from 1.50%/y to 4.95%/y with aspirin cotreatment (*P*=0.004); for ximelagatran, the annual major bleeding rate increased from

<table>
<thead>
<tr>
<th>TABLE 3. Primary Event Rates for Ximelagatran and Warfarin With and Without Concomitant Aspirin Therapy (ITT Population)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Events</strong></td>
</tr>
<tr>
<td>Aspirin+ximelagatran</td>
</tr>
<tr>
<td>Aspirin+warfarin</td>
</tr>
<tr>
<td>Aspirin ximelagatran-warfarin</td>
</tr>
<tr>
<td>No aspirin+ximelagatran</td>
</tr>
<tr>
<td>No aspirin+warfarin</td>
</tr>
<tr>
<td>No aspirin ximelagatran-warfarin</td>
</tr>
</tbody>
</table>

*ITT indicates intention to treat.*

**As per the Central Event Adjudication Committee.**
2.35% to 5.09% with aspirin cotreatment (\(P = 0.046\)). The major bleeding was almost exclusively systemic rather than intracerebral in these studies for patients on combination aspirin/anticoagulation (see earlier section). Figure 2 shows the primary event and major bleeding rates with anticoagulation therapy alone compared with combination therapy.

**Adverse Events: Liver Enzymes**

Elevation of serum alanine aminotransferase to >3 times the upper limit of normal was seen in 6% of all patients treated with ximelagatran versus 1% of patients treated with warfarin.\(^1\)\(^2\)\(^,\)\(^1\)\(^4\) For patients with prior stroke/TIA, the rates were 7% with ximelagatran versus 0% with warfarin. The corresponding values for patients without prior stroke/TIA were 6% and 1%, respectively. There were 0.4% and 0% of patients with alanine aminotransferase levels >5 times the upper limit of normal in warfarin-treated patients with and without prior stroke/TIA, respectively, whereas 4% of patients with prior stroke/TIA and 3% of patients without prior stroke/TIA had elevations of this degree with ximelagatran. These elevations typically occurred in the first 6 months and returned to normal with or without cessation of ximelagatran.

**Discussion**

For AF patients with a history of stroke/TIA and contraindications to warfarin, the currently recommended alternative is aspirin. However, aspirin is substantially less effective than warfarin for prevention of ischemic stroke in AF patients.\(^3\)\(^\text{–7}\) For example, the European Atrial Fibrillation Trial Study group showed that in patients with AF and prior stroke/TIA, the annual risk of any stroke was 4%/y for warfarin (open-label, INR 2.5 to 4.0), 10%/y for aspirin (300 mg/d), and 12% for placebo. The difference between warfarin and placebo was significant, but aspirin did not differ from placebo.\(^7\) Warfarin is highly effective for stroke prevention but is underused and difficult to manage.\(^1\)\(^7\)\(^–\)\(^2\)\(^0\) Therefore, there is a substantial need for alternative antithrombotic therapies for patients with AF. In patients with AF, a prior stroke or TIA confers the greatest risk for recurrent stroke or SEE.\(^2\)\(^,\)\(^3\)

For the practicing clinician, stroke patients are challenging to treat with warfarin: laboratory testing is burdensome because of their decreased mobility; communication of laboratory results and warfarin dosing can be hampered by patient aphasia or memory loss; stroke patients may fall, thereby increasing the risk of trauma and bleeding; and these patients often have a protracted history of hypertension and diabetes that can damage cerebral vessels and increase the risk of cerebral hemorrhage.

Our findings regarding the efficacy of ximelagatran in AF patients with prior stroke/TIA are quite encouraging. Among these high-risk patients, 97.2% who were randomized to receive ximelagatran remained free of stroke or SEE each year compared with 96.7% of patients randomized to receive adjusted-dose warfarin (Table 2). The benefit of treatment with ximelagatran was sustained throughout the duration of the study (Figure 1). As expected, patients with prior stroke or TIA were at higher risk of a primary event (stroke or SEE) compared with patients without prior stroke/TIA (Table 2). In the SPAF III trial,\(^8\) the rate of primary events (ischemic stroke and SEE) for patients with prior stroke/TIA randomized to receive dose-adjusted warfarin (target INR 2 to 3) was 3.4%/y, similar to our results (3.3%/y).

Bleeding rates, other than hemorrhagic stroke, were a secondary outcome measure for both SPORTIF trials and an important measure of safety. In a recent meta-analysis of AF

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**Table 4. Stroke/SEE, Analysis of Potential Prognostic Factors, Stepwise Model Selection Algorithm for the ITT Population**

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>Lower</th>
<th>Upper</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>0.87</td>
<td>0.54</td>
<td>1.40</td>
<td>0.5630</td>
</tr>
<tr>
<td>Aspirin use</td>
<td>1.62</td>
<td>0.99</td>
<td>2.67</td>
<td>0.0568</td>
</tr>
<tr>
<td>Age &gt;75 years</td>
<td>1.81</td>
<td>1.12</td>
<td>2.92</td>
<td>0.0153</td>
</tr>
<tr>
<td>Study</td>
<td>2.76</td>
<td>1.61</td>
<td>4.70</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

ITT indicates intention to treat. Treatment was included into the model together with other factors remaining significant at the 5%-level after stepwise model selection. Aspirin use was not randomized.
trials, major extracranial hemorrhage rates with warfarin were 0.9%/y. In SPAF II, annual rates of major bleeding with warfarin treatment were 1.7% in patients aged ≤75 years and 4.2% in patients aged >75. In our study, major bleeding rates in warfarin-treated patients with prior stroke/TIA were 1.5%/y for those not taking aspirin and 4.95%/y for those who were (Figure 2).

Liver enzyme (alanine aminotransferase) elevations >3 times the upper limit of normal occurred more frequently in patients treated with ximelagatran (6%) than with warfarin (1%). The liver enzyme elevations were most often detected in the first 6 months of treatment and resolved either spontaneously with ongoing treatment or after cessation of ximelagatran. Adverse hepatic effects have also been observed in a recent postmarketing study of this agent for deep venous thrombosis. The sponsor (AstraZeneca) has voluntarily withdrawn this product from the European market, where it was approved for short-term prevention of deep venous thrombosis after orthopedic surgery.

An area of uncertainty in secondary stroke prevention is whether dual therapy with 2 antithrombotic agents offers benefits that exceed bleeding risks. We failed to demonstrate any association between using an aspirin-anticoagulation combination and a reduction in primary outcome events (Table 3). In fact, despite controlling for other risk factors, patients on combination aspirin-anticoagulation therapy tended to have higher stroke rates (Table 4). We cannot exclude the possibility that the treating physicians placed the highest-risk patients on combination aspirin-warfarin treatment based on uncontrolled risk factors.

Combination antithrombotic therapy clearly increased bleeding complications (Figure 2) in AF patients with prior stroke/TIA. This finding was also confirmed in the pooled analysis of all SPORTIF III and V patients. The risk of bleeding with combined aspirin-warfarin compared with warfarin alone has been investigated previously in elderly patients with AF, and results similar to ours have been reported. Also, when compared with aspirin alone, the combination of aspirin plus warfarin has been shown to increase major bleeding risk in post-myocardial infarction secondary prevention trials.

In conclusion, for AF patients with a history of stroke/TIA, ximelagatran provides protection from stroke andSEE comparable to that of closely monitored warfarin therapy. Major bleeding complications, especially intracranial hemorrhages, were infrequent with ximelagatran and compared favorably with warfarin. The adverse hepatic effects of this oral direct thrombin inhibitor have limited its clinical utility; nonetheless, the SPORTIF trials and results demonstrate the therapeutic potential for this emerging new class of agents. Combining low-dose aspirin with either anticoagulant was not associated with a reduction in thromboembolic events, and bleeding rates were substantially higher. Therefore, we do not currently advocate combining antithrombotic therapy with aspirin in high-risk patients with AF.

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Disclosures
Hans-Christoph Diener, MD, and Stefan G. Spitzer, MD, are investigators in the SPORTIF III study. Paul T. Akins, MD, PhD, Gregory W. Albers, MD, Harvey A. Feldman, MD, David Newman, MD, and Robert G. Zoble, MD, PhD, are investigators in the SPORTIF V study. Gregory W. Albers, MD, and Hans-Christoph Diener, MD, are members of the SPORTIF Executive Steering Committee.

References
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