ONVALVULAR ATRIAL FIBRIL-
lation is implicated in nearly
15% of strokes.1 By meta-
analysis of 6 randomized
trials, dose-adjusted warfarin de-
creases stroke risk by 62%.2,3 In prac-
tice, the risk of bleeding limits treat-
ment with warfarin, particularly among
the elderly. Variability of anticoagula-
tion intensity from interactions with
foods and medications necessitates fre-
quent monitoring and dose adjust-
ments yet leaves patients outside the
therapeutic range almost half the time.5,6
Underuse of warfarin in patients with
atrial fibrillation at high risk of bleed-
ing calls for safer, more dependable
alternatives.7,8

The direct thrombin inhibitor
ximelagatran offers fixed oral dosing
without need for coagulation monitor-
ing, rapid onset and offset of action, stable pharmacokinetics with little poten-
tial for drug interactions, and no
known food interactions.8-12 The
SPORTIF (Stroke Prevention using an
Oral Thrombin Inhibitor in Atrial Fi-
brillation) program included 2 long-
term trials comparing ximelagatran to
warfarin for prevention of thromboem-
bolism in patients with atrial fibrilla-
tion. The open-label SPORTIF III study

See also pp 681, 699, and 736.
found ximelagatran at least as effective as warfarin. This report describes SPORTIF V, based on the same protocol except that anticoagulation was administered in a double-blinded manner.

**METHODS**

The rationale, design, and patient characteristics of the SPORTIF V trial have been previously described. Briefly, the trial compared fixed-dose oral ximelagatran with adjusted-dose warfarin for prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation requiring chronic anticoagulant therapy. The executive steering committee developed the protocol, guided study execution masked to treatment allocation, and prepared results for publication with unrestricted access to data. The sponsor provided 2 of the 8 voting members.

**Patients**

Written consent was required from each patient according to a protocol approved by local institutional review boards and compliant with the Declaration of Helsinki. Between August 2, 2000, and December 7, 2001, a total of 3922 patients were randomized at 409 sites in the United States and Canada, including academic and nonacademic offices and clinics attended by both general practitioners and specialists. Entry criteria were based on current guidelines for anticoagulation and required at least 1 of the following risk factors in addition to persistent or paroxysmal nonvalvular atrial fibrillation: previous stroke, transient ischemic attack, or systemic embolism, hypertension, left ventricular dysfunction (ejection fraction <40% or symptomatic systolic or diastolic heart failure), aged 75 years or older, or aged 65 years or older with known coronary disease or diabetes mellitus. Race and ethnicity were classified according to self-report.

**Treatment Allocation**

Treatment was randomized to either adjusted-dose warfarin, target international normalized ratio (INR) 2.0 to 3.0, or fixed-dose ximelagatran, 36 mg twice daily, according to a centralized adaptive allocation algorithm that balanced groups according to concurrent aspirin use at entry and previous thromboembolism. Using a double-dummy design to maintain blinding, all patients received both assigned anticoagulant and placebo and underwent blood sampling at intervals of 31 days or fewer. Most INR measurements (86%) were made by finger-stick sampling using uniform point-of-care devices (ProTime, Microcoagulation System, International Technidyne Corp, Edison, NJ). Another 14% were performed at a commercial laboratory (Quest Diagnostics Inc, Van Nuys, Calif); fewer than 1% involved local laboratories, with results reported to unblinded personnel not engaged in patient management or assessment. Warfarin dose was based on actual INR results, with adherence estimated by linear interpolation as proportion of time in the therapeutic range.

For patients assigned to ximelagatran, sham INR values were generated to mimic variations on warfarin; compliance was estimated by tablet counts. Aspirin was permitted in doses up to 100 mg daily, but nonsteroidal anti-inflammatory medication was limited to 7 days or fewer per month. Other antithrombotic medications were prohibited.

**End Points and Assessments**

The primary end point was all strokes (ischemic or hemorrhagic) and systemic embolic events. After randomization, patients were seen at weeks 1, 4, and 6; months 2, 3, 4, 5, 6, 8, 10, and 12; and every 3 months thereafter. Primary events were evaluated as early as feasible based on clinical findings and brain imaging. Detection was

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**Box. Adjudicated Events and End Point Definitions**

**Events**

- **Stroke**: Abrupt onset of a focal neurological deficit in the distribution of a brain artery persisting more than 24 hours or due to intracerebral hemorrhage.
- **Death**: Transient ischemic attack: Abrupt onset of a focal neurological deficit in the distribution of a brain artery persisting less than 24 hours.
- **Systemic embolic event (SEE)**: Abrupt vascular insufficiency associated with clinical and radiological evidence of arterial occlusion in the absence of another likely mechanism.
- **Acute myocardial infarction**: At least 2 of the following: (1) typical chest pain for at least 20 minutes; (2) electrocardiogram showing changes of acute myocardial infarction; and (3) cardiac enzyme elevation more than twice the upper limit of normal.
- **Major bleeding**: Bleeding that was fatal or clinically overt and associated with either transfusion of 2 units or more of blood or a 20-g/L or more decrease in hemoglobin or bleeding that was intracranial, retroperitoneal, spinal, ocular, pericardial, or atraumatic articular. (Intracranial bleeding excludes intracerebral hemorrhages, which were counted as primary events.)

**End Points**

**Primary**: Stroke (ischemic or hemorrhagic) and SEE.

**Secondary**

1. Stroke, SEE, death, acute myocardial infarction
2. Ischemic stroke, transient ischemic attack, SEE
3. Major bleeding
4. Major and bleeding

*The central event adjudication committee categorized strokes as ischemic or hemorrhagic.
†Reported by local investigators but did not satisfy criteria for major bleeding.
enhanced by administering a stroke-symptom questionnaire every 6 months. Positive responses prompted evaluation by study-affiliated neurologists who were blinded to treatment. An independent, blinded, central event adjudication committee reviewed the reports. Stroke severity was assessed 3 months after an event, according to the modified Rankin20 and Barthel indices.21

Because in an earlier study22 4.3% of patients taking ximelagatran developed serum alanine aminotransferase (ALT) concentrations higher than 3 times the upper limit of normal (ULN), liver function (ALT, aspartate aminotransferase, alkaline phosphatase, and total bilirubin) was tested at least monthly for 6 months, then bimonthly for the first year, and then quarterly. Weekly testing was required if any value exceeded 3 times the ULN, and drug discontinuation was required if a value exceeded 3 times the ULN for 4 weeks or 7 times the ULN at any time or clinical hepatotoxicity developed. In October 2001, limits were modified to twice the ULN for weekly testing and 5 times the ULN for drug dis-continuation.

**Statistical Analyses**

The primary analysis compared treatment efficacy for first occurrence of a primary event among all randomized patients according to the intention-to-treat (ITT) principle, assuming a constant event rate over time. The objective was to establish whether ximelagatran was noninferior23 to warfarin within an absolute margin of 2.0% per year for the difference in rates of primary events.14,24 This margin was based on the expected rate during warfarin therapy and a prespecified judgment about clinically meaningful difference. The criteria required that the upper bound of the 1-sided 97.5% confidence interval (CI) for the difference in event rates not exceed 2.0% per year. The \( P \) value for noninferiority is the probability of incorrectly rejecting the prespecified null hypothesis that the true difference between event rates (ximelagatran-warfarin) exceeds 2% per year.

The ITT analysis included all patients, regardless of adherence, with exposure truncated at last contact. Confirmatory sensitivity analyses included all-cause mortality in addition to the primary end point and on-treatment analysis of the primary end point excluding events beyond 30 consecutive or 60 cumulative days off randomized treatment. Accumulation of primary events and deaths continued until study closure, even if assigned treatment was stopped, whereas other events were recorded during the period on treatment. Unless otherwise stated, analyses of end points composed of only stroke, systemic embolism, or death were based on ITT; other analyses used the on-treatment approach. All analyses were performed using SAS version 8.2 software (SAS Institute, Cary, NC) and are reported as the number of patients experiencing each event or composite.

The protocol stipulated exposure of at least 12 months per patient, at least 4000 patient-years of aggregate follow-up, and at least 80 patients with verified primary events. This provided 90% power to demonstrate noninferiority for aggregate primary event rates of 4.0% per year or less, based on 1-sided \( \alpha = 0.025 \). The data and safety monitoring board conducted interim analyses at approximately 12.5%, 25%, 50%, and 75% of total exposure. The Lan-DeMets quadratic \( \alpha \) spending function guided safety monitoring.25 This group sequential stopping rule was applied only for negative trends along safety parameters prespecified before accessing unblinded data. Interim analyses for the primary end point were guided by the Haybittle-Peto group sequential boundaries, requiring no adjustments to the final analysis.26,27 Based on analysis of the event rate after 50% of exposure elapsed, the data safety monitoring board recommended extension of accrual to accumulate the requisite number of events.

**RESULTS**

**Patients and Follow-up**

The study included 3922 patients randomly assigned, including 3 of 1960 without qualifying risk factors in the ximelagatran group and 4 of 1962 in the warfarin group (FIGURE 1). This resulted in a net exposure of 6405 patient-years for the primary outcome. Nine pa-
tients assigned to receive warfarin and 6 to receive ximelagatran did not take either study drug. Although none developed end point events, all were included in ITT analyses. Ninety-six percent of patients were white; 69%, men; 2193 (56%), previous smokers; and 2314 (59%) denied regular alcohol use. The mean (SD) age was 72 (9.1) years; weight averaged 90 (22) kg; 95 (20) kg for men and 78 (20) kg for women. Of the total study population, 1658 patients (42%) were aged at least 75 years, 3307 (84%) had atrial fibrillation for at least a year, and 3367 (86%) had persistent atrial fibrillation. In addition to atrial fibrillation, 2916 patients (74%) had 2 or more stroke risk factors. Before entry, 3278 patients (84%) were taking a vitamin K antagonist (usually warfarin); 719 (18%), acetylsalicylic acid; 1909 (49%), a β-adrenergic antagonist; 1875 (48%), an angiotensin-converting enzyme inhibitor; 1442 (37%), a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin); and 177 (4.5%), amiodarone. During the study, patients took a median of 12 other prescribed medications. Clinical characteristics were balanced between treatment groups (Table 1) and were similar to cohorts in earlier trials demonstrating superiority of warfarin over placebo for prevention of atrial fibrillation–related stroke.13,14

In patients assigned to receive warfarin, the mean (SD) INR across all measurements was 2.4 (0.8). Values fell within target range (2.0–3.0) for 68% of the time on treatment, below 2.0 for 20%, above 3.0 for 12%, and between 1.8 and 3.2 for 83%. Anticoagulation intensity was within target range at least half the time on treatment in 1667 patients (85%) assigned to receive warfarin. For 1389 patients (71%) receiving ximelagatran, compliance was 90% or higher, and sham INR values averaged a mean (SD) of 2.4 (0.6) over more than 38,000 measurements.

Mean (SD) follow-up was 20 (3.1) months in both treatment groups (overall median, 20; range, 0–31 months), yielding 3212 patient-years at risk in the warfarin group and 3193 in the ximelagatran group. Thirty-five percent of patients prematurely stopped treatment, 640 (33%) assigned to receive warfarin and 718 (37%) assigned to receive ximelagatran (P = .01). At the end of the trial, special efforts to ascertain the vital status of 226 patients (6%) who interrupted follow-up disclosed no additional cases of stroke and 8 deaths in 104 of 119 patients assigned to receive ximelagatran (status remained unknown for 15) and none with stroke and 7 deaths in 99 of 107 such patients in the warfarin group (8 unknown). A total of 137 patients (7.0%) in the warfarin group and 130 (6.6%) in the ximelagatran group stopped assigned treatment when end points occurred. In the warfarin group, 205 (10.6%) chose to stop treatment and 175 (8.9%) stopped because of adverse events compared with 197 (10.0%) and 238 (12.1%), respectively, with ximelagatran, the latter due mainly to elevation of serum transaminase enzymes.

### Treatment Outcomes

#### Primary End Points

The central event adjudication committee confirmed primary events in 37 patients assigned to receive warfarin and 51 patients assigned to receive ximelagatran, corresponding to incidence rates of 1.16% and 1.61% per year, respectively (P = .13 for a difference between treatments). The P value for noninferiority, that is, the probability of incorrectly rejecting the prespecified null hypothesis that the true difference between event rates (ximelagatran-warfarin) exceeds 2% per year was lower than .001. The upper bound of the 95% confidence interval (CI) surrounding the difference of 0.45% per year was 1.03, well below the specified margin of 2.0% per year.

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Table 1. Characteristics of Randomized Patients According to Randomized Treatment Assignment*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ximelagatran (n = 1960)</th>
<th>Warfarin (n = 1962)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men, No. (%)</td>
<td>1365 (70)</td>
<td>1353 (69)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>71.6 (9.2)</td>
<td>71.6 (9.0)</td>
</tr>
<tr>
<td>Body weight, mean (SD), kg</td>
<td>90.1 (21.9)</td>
<td>89.1 (21.3)</td>
</tr>
<tr>
<td>Body mass index, mean (SD)†</td>
<td>30.0 (6.6)</td>
<td>29.6 (6.2)</td>
</tr>
<tr>
<td>Race, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1875 (95.7)</td>
<td>1888 (96.2)</td>
</tr>
<tr>
<td>Black</td>
<td>67 (3.4)</td>
<td>58 (3.0)</td>
</tr>
<tr>
<td>Asian</td>
<td>15 (0.8)</td>
<td>10 (0.5)</td>
</tr>
<tr>
<td>Aspirin at entry, No. (%)</td>
<td>352 (18)</td>
<td>367 (19)</td>
</tr>
<tr>
<td>VKA at entry, No. (%)</td>
<td>1617 (83)</td>
<td>1661 (85)</td>
</tr>
<tr>
<td>Systolic BP, mean (SD), mm Hg</td>
<td>133 (18)</td>
<td>132 (18)</td>
</tr>
<tr>
<td>Atrial fibrillation onset &lt;1 y, No. (%)</td>
<td>311 (16)</td>
<td>304 (15)</td>
</tr>
<tr>
<td>Paroxysmal atrial fibrillation, No. (%)</td>
<td>282 (14)</td>
<td>270 (14)</td>
</tr>
<tr>
<td>Risk factors, No. (%) ‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>490 (25)</td>
<td>509 (26)</td>
</tr>
<tr>
<td>2</td>
<td>600 (31)</td>
<td>597 (30)</td>
</tr>
<tr>
<td>≥3</td>
<td>867 (44)</td>
<td>852 (44)</td>
</tr>
<tr>
<td>Previous stroke and/or TIA, No. (%)</td>
<td>369 (19)</td>
<td>348 (18)</td>
</tr>
<tr>
<td>Previous non-CNS embolism, No. (%)</td>
<td>92 (4.7)</td>
<td>85 (4.3)</td>
</tr>
<tr>
<td>Age ≥75 y, No. (%)</td>
<td>838 (43)</td>
<td>820 (42)</td>
</tr>
<tr>
<td>Hypertension, No. (%)</td>
<td>1584 (81)</td>
<td>1582 (81)</td>
</tr>
<tr>
<td>CHF/LV dysfunction, No. (%)</td>
<td>735 (38)</td>
<td>788 (40)</td>
</tr>
<tr>
<td>Age ≥65 y + CAD, No. (%)</td>
<td>822 (42)</td>
<td>803 (41)</td>
</tr>
<tr>
<td>Age ≥65 y + diabetes mellitus, No. (%)</td>
<td>389 (20)</td>
<td>373 (19)</td>
</tr>
</tbody>
</table>

*Abbreviations: BP, blood pressure; CAD, coronary artery disease; CHF, congestive heart failure; CNS, central nervous system; LV, left ventricular; TIA, transient ischemic attack; VKA, vitamin K antagonist.

†Body mass index is calculated as weight in kilograms divided by the square of height in meters.

‡Risk factors are listed under “Patients” in the “Methods” section.

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Of primary events among patients assigned to warfarin, 37 were ischemic strokes, 2 were hemorrhagic strokes, and 1 was systemic embolism; 3 patients had multiple events. In the patients assigned to receive ximelagatran, there were 49 ischemic strokes, 2 hemorrhagic strokes, and 6 systemic embolic events; 6 patients experienced multiple events (TABLE 2).

The secondary on-treatment analysis discounted events occurring after treatment cessation in 9 patients assigned to receive warfarin and 10 assigned to receive ximelagatran, rates of 1.02% and 1.57% per year, respectively, difference 0.55% per year (95% CI, −0.06% to 1.2% per year). Results were similar using a shorter 10-day period off-treatment (event rate difference, 0.44% per year; 95% CI, −0.14% to 1.01% per year). Among those taking warfarin, all 28 primary events were ischemic strokes; one patient also developed hemorrhagic stroke. In the 23 patients with values available within 30 days of ischemic stroke, INR was no more than 2.0 in 9 (39%). Among 41 patients developing primary events while taking ximelagatran, there were 35 ischemic strokes, 1 hemorrhagic stroke, and 6 systemic embolic events (1 patient had multiple events).

Secondary End Points. Fifty-two patients taking warfarin experienced ischemic stroke, transient ischemic attack, or systemic embolism (1.9% per year) compared with 67 given ximelagatran (2.6% per year; \( P = .12 \); on-treatment analysis; Table 2). There were 123 deaths (3 fatal strokes) in the warfarin group and 116 (10 fatal strokes) in the ximelagatran group (ITT analysis). Nonfatal disabling stroke (modified Rankin score \( \geq 3 \) or Barthel index <60) occurred in 7 patients in the warfarin group and 6 in the ximelagatran group. Composite rates for all-cause mortality plus primary events were 4.7% and 4.8% per year, respectively. The composite end point of stroke, systemic embolism, myocardial infarction, or death occurred in 119 patients taking warfarin (4.3% per year) and 110 taking ximelagatran (4.2% per year; \( P = .84 \)).

(Figure 2).
Hemorrhage. Hemorrhagic strokes (included as primary events) occurred in 2 patients in each group (0.06% per year; Table 3). Seven patients in the warfarin group and 5 in the ximelagatran group developed subdural hematoma. Major extracerebral bleeding occurred in 84 patients assigned to the warfarin group (3.1% per year) and in 63 assigned to the ximelagatran group (2.4% per year), a reduction of 0.66% per year (95% CI, –1.55% to 0.23% per year). Of confirmed major hemorrhages, bleeding was fatal in 1 patient assigned to the warfarin and 2 assigned to the ximelagatran groups. Decreased hemoglobin accounted for 41% and transfusion for 5% of major bleeding; proportions were similar in both treatment groups. Among the 84 patients in the warfarin group with major bleeding, INR exceeded 3.0 in 20 cases. Considering minor plus major hemorrhages, there was significantly more bleeding among patients receiving warfarin (903 patients, 47% per year) than ximelagatran (737 patients, 37% per year; relative risk reduction 21%; 95% CI, –14 to –6.0% per year; for the difference, P < .001). The 571 patients (15%) who took aspirin (≤100 mg/d) along with the anticoagulant at any time during the trial had higher overall (major and minor) bleeding rates (41% per year with ximelagatran, 69% per year with warfarin) than those not taking aspirin (37% per year with ximelagatran, 44% per year with warfarin).

Other Adverse Events. Adverse events other than bleeding occurred with equal frequency in both groups (Table 3). In 117 patients (6.0%) taking ximelagatran, serum ALT levels rose to higher than 3 times ULN compared with 15 patients taking warfarin (0.8%; P < .001). Elevations typically occurred between 2 and 6 months after initiating treatment and returned toward baseline without clinical sequelae either spontaneously (45 patients) or after treatment cessation (68 patients). Alanine aminotransferase levels returned to below the ULN in all but 5 patients, including 1 who died 3 days after repair of an iliac artery aneurysm, 1 whose serum ALT level of 165 U/L and bilirubin level was normal 2 weeks before death from ischemic heart disease, and 1 for whom no follow-up information could be obtained. The other cases are discussed below.

Within 30 days of ALT concentration elevation higher than 3 times the ULN, total serum bilirubin concentration rose above twice the ULN in 9 patients taking ximelagatran and 1 taking warfarin. One patient with serum ALT higher than 3 times ULN 85 days after beginning ximelagatran treatment displayed hepatic necrosis on liver biopsy result 20 days after stopping the drug. This patient died 145 days after random assignment following corticosteroid treatment; autopsy revealed resolving hepatitis (nodular islands of regenerating hepatocytes without active inflammation) and hemorraghic perforation of a duodenal ulcer. Another patient whose serum ALT concentrations reached 11 times the ULN with ximelagatran (total serum bilirubin, 1.6 mg/dL [27.4 µmol/L], 1.45 times the ULN) developed fatal gastrointestinal hemorrhage.

COMMENT

In this double-blind trial involving relatively high-risk patients with nonvalvular atrial fibrillation, the direct thrombin inhibitor ximelagatran was noninferior to well-controlled warfarin within the prespecified margin of 2.0% per year for prevention of stroke and systemic embolism. The difference in primary event rates between treatments was 0.45% per year in the ITT model, and the upper bound of the 95% CI surrounding this difference was 1.03% per year. Hence, the probability of rejecting noninferiority was < .001 for the specified margin (2.0% per year) and 0.06 for a margin of 1.0% per year. Although the warfarin dose was regulated to maintain anticoagulation within a narrow range while ximelagatran was administered in fixed dose without anticoagulation monitoring, there was no increase in bleeding (indeed, less minor bleeding) with ximelagatran.

Thrombin plays a pivotal role in fibrin formation and activation of platelets and other coagulation factors in a variety of cardiovascular diseases. Although anticoagulants such as warfarin and heparin inhibit thrombin indirectly, ximelagatran, rapidly converted to melagatran after oral administration, inhibits soluble and fibrin-bound thrombin directly.28,29 In previous studies, ximelagatran compared favorably with warfarin or low-molecular-weight heparin for prevention and treatment of venous thromboembolism30,31 and in combination with aspirin was superior to aspirin alone for prevention of ischemic events in patients with acute coronary syndromes.32 The well-established and accepted efficacy of warfarin for prevention of

### Table 3. Other Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Ximelagatran (n = 1953)</th>
<th>Warfarin (n = 1953)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No. of patients with adverse events</td>
<td>1827 (93.5)</td>
<td>1834 (93.9)</td>
</tr>
<tr>
<td>Purpura</td>
<td>298 (15.3)</td>
<td>428 (21.9)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>327 (16.7)</td>
<td>312 (16.0)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>240 (12.3)</td>
<td>242 (12.4)</td>
</tr>
<tr>
<td>Edema</td>
<td>207 (10.6)</td>
<td>247 (12.6)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>229 (11.7)</td>
<td>222 (11.4)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>151 (7.7)</td>
<td>282 (14.4)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>197 (10.1)</td>
<td>224 (11.5)</td>
</tr>
<tr>
<td>Hypertransaminasemia†</td>
<td>117 (6.0)</td>
<td>15 (0.8)</td>
</tr>
<tr>
<td>Hematuria</td>
<td>109 (5.6)</td>
<td>105 (5.4)</td>
</tr>
</tbody>
</table>

*Selected adverse events shown occurred in 5% or more of the ximelagatran cohort who took at least one dose of study drug. Individual patients are counted once for each adverse event.
†Serum alanine-aminotransferase concentration higher than 3 times the upper limit of normal.
thromboembolism in high-risk patients with nonvalvular atrial fibrillation made a placebo-controlled study unethical; hence, the protocol was based on noninferiority analysis using an active control.\textsuperscript{14,24} The primary analysis demonstrating comparable efficacy was sustained when all-cause mortality was included or primary events were evaluated by on-treatment analyses. Although there were fewer events in the warfarin group, the absolute difference of <0.5% per year was not statistically significant. There was a lower rate of total bleeding with ximelagatran but no significant difference in major hemorrhage rates.

Secondary efficacy analyses mirror the primary analysis. The composite of all stroke, systemic embolism, death, and myocardial infarction occurred with similar frequency in both groups, as did a composite limited to ischemic events. Consistency in both primary and secondary end points strengthens confidence in the noninferiority assessment.

Enrolled patients represented those typical in clinical practice, bearing considerable cardiovascular comorbidity as reflected in their advanced age, stroke risk profiles, and concurrent medications. Even so, rates of thromboembolism were low, 1.4% per year overall. Among high-risk cohorts in previous trials, thromboembolism rates were more than 7% per year without anticoagulation\textsuperscript{15} and 2.4% per year with warfarin (range, 0.6%–3.1% per year).\textsuperscript{2} The quality of anticoagulation control with warfarin was better in our trial than in previous studies and seldom achieved in practice but comparable with SPORTIF III.\textsuperscript{13} The low warfarin event rate\textsuperscript{2,14} may reflect better dose regulation, control of hypertension or hyperlipidemia, other differences in patient characteristics or management, or chance.

Rates of intracerebral hemorrhage during treatment were exceptionally low, but extracerebral hemorrhage was more frequent than in other randomized trials. This reflects the criterion of declining hemoglobin of 2 g/dL or higher, without which major bleeding was 2.1% per year in the warfarin group, comparable with previous studies,\textsuperscript{2} and 1.6% per year in the ximelagatran group (P = .22). Liberal reporting criteria for minor bleeding may have captured some episodes of little clinical importance.

The combination of low rates of stroke and cerebral hemorrhage might be explained by control of hypertension. Mean systolic blood pressure was 133 mm Hg even though 80% of patients had a history of hypertension at entry. In a recent trial involving patients with atrial fibrillation, lowering systolic blood pressure by 9 mm Hg reduced ischemic stroke by nearly 30% and halved the rate of intracerebral hemorrhage.\textsuperscript{36} Control of hypertension seems to be a critically important adjunct to antithrombotic therapy to avoid adverse neurological outcomes in patients with atrial fibrillation.

The incidence of serum ALT concentration elevations higher than 3 times the ULN (6.0%) was similar to that in previous clinical trials of ximelagatran.\textsuperscript{13,22,33} This reaction typically occurred 1 to 6 months after initiation and then normalized, whether or not treatment continued. In at least 1 case, however, severe hepatitis developed with fatal gastrointestinal hemorrhage. Despite extensive investigation, the mechanism of ALT elevation remains unknown, though numerous types of reactions known to cause hepatotoxicity have been excluded.\textsuperscript{17,38} Surveillance of serum enzymes prior to and during therapy is necessary to exclude patients with elevated levels and minimize the risk of hepatotoxicity.

Ximelagatran is eliminated mainly through renal clearance, and patients with a creatinine clearance lower than 30 mL/min (0.501 mL/s) were excluded. The relative safety and efficacy of ximelagatran and warfarin should not be extrapolated to patients with valvular heart disease, pregnancy, or severe renal insufficiency or to those undergoing cardioversion of atrial fibrillation without additional experience in these clinical situations.

The SPORTIF V trial is the largest yet reported trial involving patients with atrial fibrillation for prevention of stroke and systemic embolism. Low rates of thromboembolism and bleeding occurred when ximelagatran was given in a fixed dose without anticoagulation monitoring. Further investigation is needed to clarify the risk of serious hepatic reactions and identify predictive features to select appropriate patients for treatment with ximelagatran. In the balance are a large number of potentially preventable fatal or disabling strokes that accumulate as a consequence of the limitations and underutilization of warfarin.

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\textbf{Author Contributions:} Dr Halperin, as a principal investigator of this trial, had complete access to all of the data and takes responsibility for the integrity of the data and the accuracy of the data analyses. An independent data and safety monitoring board (DSMB) that included academic statisticians, no employees of the sponsor oversaw patient safety, had access to all data, and independently confirmed the results at an independent statistical center at the Uni- versity of Wisconsin under the direction of David DeMets, PhD.

\textbf{Study concept and design:} Albers, Diener, Frison, Grind, Halperin, Horrow, Nevinson, Olsson, Partridge, Petersen, Vahanian.

\textbf{Acquisition of data:} Albers, Diener, Frison, Grind, Halperin, Horrow, Nevinson, Olsson, Partridge, Petersen, Vahanian.

\textbf{Analysis and interpretation of data:} Albers, Diener, Frison, Grind, Halperin, Horrow, Nevinson, Olsson, Partridge, Petersen, Vahanian.

\textbf{Critical revision of the manuscript:} Albers, Diener, Frison, Grind, Halperin, Horrow, Nevinson, Olsson, Partridge, Petersen, Vahanian.

\textbf{Statistical analysis:} Albers, Diener, Frison, Grind, Halperin, Horrow, Nevinson, Olsson, Partridge, Petersen, Vahanian.

\textbf{Study funding:} AstraZeneca research funds provided for study personnel, equipment, and supplies. AstraZeneca was responsible for the study design, collection, and analysis of the data. AstraZeneca had access to the data and takes responsibility for the integrity of the data and the accuracy of the data analyses.

\textbf{Previous presentation:} This study was presented in part at the American Heart Association 59th Scientific Sessions, New Orleans, La, November 1999.
XIMELAGATRAN IN ATRIAL FIBRILLATION

In "Ximelagatan in Atrial Fibrillation," the editorial board of the journal discusses the medication's potential for cytochrome P450-mediated drug-drug interactions and pharmacokinetics and pharmacodynamics of ximelagatran, a novel direct thrombin inhibitor in patients with nonvalvular atrial fibrillation. The study was conducted to determine the safety and efficacy of ximelagatran compared with warfarin in patients with nonvalvular atrial fibrillation (SPORTIF III). The study was funded by AstraZeneca. The Conseil Medical du Canada, on behalf of the Executive Steering Committee, prepared, reviewed, and approved the manuscript. The editorial board of the journal highlights the importance of the study and its implications for clinical practice.

REFERENCES


7. Halperin JL. The Executive Steering Committee on behalf of the SPORTIF III and V Study Investigators. Role of the Sponsor: the AstraZeneca, participated in the design and conduct of the study. The sponsors collected and managed the data, the sponsor and the data and safety monitoring board performed the analysis of the data, and the executive steering committee interpreted the data. The executive steering committee prepared, reviewed, and approved the manuscript.

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XIMELAGATRAN IN ATRIAL FIBRILLATION


Science may have found a cure for most evils, but it has found no remedy for the worst of them all—the apathy of human beings.
—Helen Keller (1880-1968)