Ximelagatran or Warfarin for Stroke Prevention in Patients With Atrial Fibrillation?

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Up to one sixth of all ischemic strokes are attributable to atrial fibrillation (AF). This proportion is likely to increase in the future as the prevalence of AF increases with the progressive “aging” of the population.

The only 2 treatments that effectively reduce the risk of stroke among individuals with AF are aspirin (relative risk reduction [RRR]: 22%; 95% CI: 2% to 38%) and adjusted-dose oral anticoagulation with the vitamin K antagonist, warfarin (RRR: 62%; 95 CI: 48% to 72%). Heart rhythm control, by means of cardioversion, although intuitively attractive, has not been shown to be more effective than rate control combined with oral anticoagulation. Omitting the left atrial appendage using catheter techniques, and surgical excision of the left atrial appendage have not been evaluated in controlled trials and are not widely applicable.

The main limitation of aspirin is that it is only modestly effective in preventing stroke among patients in AF compared with placebo (RRR: 22%) and with oral anticoagulation (warfarin versus aspirin: RRR 45%; 95% CI: 29% to 57%).

The main limitation of warfarin is that it causes twice as many intracranial and extracranial hemorrhages as aspirin, particularly in patients with a history of bleeding, the elderly, and those with common polymorphisms for genes encoding the hepatic microsomal enzyme CYP2C9 and the factor IX propeptide. The excess bleeding associated with warfarin can be attributed in part to its narrow therapeutic window and numerous interactions with other drugs and foods. Other practical limitations to long-term warfarin therapy are its need for regular coagulation monitoring and dose adjustment, its slow onset and offset of action, and the risk of fetal malformations. As a result, only one third to one half of patients with AF who are appropriate candidates for warfarin therapy actually receive it.

Is the Direct Thrombin Inhibitor, Ximelagatran, an Alternative to Warfarin?

Thrombin is the central enzyme in hemostasis. It is formed from prothrombin (via factor Xa), and its major activity is in the final step of coagulation, where it cleaves fibrinopeptides from fibrinogen to form fibrin. The procoagulant effects of thrombin can be blocked by inactivating the enzyme itself or by preventing its generation.

Ximelagatran (AstraZeneca), a pro-drug of melagatran, is an orally administered direct thrombin inhibitor. It is rapidly absorbed from the gut and converted to its active form, melagatran. The maximum concentration of melagatran is attained 1.6 to 1.9 hours after administration. Melagatran is not metabolized or bound to plasma proteins, and its clearance is predominantly (~80%) via the kidneys, with a half life of 4 to 5 hours. Ximelagatran therefore needs to be administered twice daily.

SPORTIF III and V Trials of Ximelagatran Versus Warfarin in AF Patients

The Stroke Prevention using the ORal direct Thrombin Inhibitor ximelagatran in patients with nonvalvular atrial Fibrillation (SPORTIF) III and V trials were phase III clinical trials. The 2 trials were conducted independently but their designs were similar in order to facilitate pooling of their results when completed. Their primary objective was to determine whether the efficacy of the oral direct thrombin inhibitor ximelagatran 36 mg twice daily, was noninferior to adjusted-dose warfarin (international normalized ratio [INR] 2.0 to 3.0) for the prevention of all strokes and systemic embolism (within a margin of 2% per year) among patients with nonvalvular AF (persistent or paroxysmal) who had at least 1 additional risk factor for stroke and a calculated creatinine clearance ≥30 mL/min.

In SPORTIF III, treatment with ximelagatran or warfarin was randomly allocated open-label to 3407 patients in 23 countries of Europe and Australasia (Australia, New Zealand, Asia). The results have been published recently. In contrast, in SPORTIF V treatment with ximelagatran or warfarin was randomly allocated double-blind to 3922 patients in the United States and Canada. The results have not been peer-reviewed and published, but were presented at the American Heart Association meeting in November 2003.

The mean duration of treatment was 17 months in SPORTIF III and 20 months in SPORTIF V. Among the patients assigned to warfarin, the INR was maintained between 2.0 and 3.0 for 66% of the entire follow-up period in SPORTIF III and 68% in SPORTIF V, and between 1.8 and 3.2 for 81% of the entire follow-up period in SPORTIF III and 83% in SPORTIF V.
Twice as many patients in the ximelagatran group experienced adverse events (mainly related to elevation of serum transaminase enzymes) than in the warfarin group.

The primary outcome measure was all stroke and systemic embolic events. Patient outcome was evaluated by a blinded local study-affiliated neurologist and a blinded central events adjudication committee.

The primary analysis was based on intention-to-treat. The prespecified threshold for noninferiority was an absolute margin of 2% per year for the difference in the rates of the primary outcome measure between ximelagatran and warfarin.

The primary efficacy and safety outcomes for the SPORTIF III and V trials are presented in the Table and pooled data for the primary efficacy outcome are presented in the Figure.

In the 7329 patients randomized in the SPORTIF III and V trials, there were a combined total 91 primary outcome events (stroke or systemic embolism) among patients allocated ximelagatran (2.5%) and 93 events among those allocated warfarin (2.5%). This is a RRR of 1% (95% CI: 95% CI: −89% to 48%), and absolute risk reduction (ARR) during the entire follow-up period of 0.1% (95% CI: −1.7 to 1.5%; P=0.92). Although there was statistical evidence of heterogeneity between the 2 trials for the primary outcome (P=0.02), both trials fulfilled the criteria for noninferiority of ximelagatran compared with warfarin.

The individual and pooled results of SPORTIF III and V therefore support the hypothesis that a fixed oral dose of ximelagatran, without coagulation monitoring, is not inferior to well-controlled, adjusted-dose warfarin in preventing stroke and systemic embolic events among high-risk patients with AF who do not have impaired renal function.21

The pooled rate of major bleeding was 2.5% among patients allocated ximelagatran and 3.4% among patients allocated warfarin (annualized rates 1.3% versus 1.8% in SPORTIF III and 2.4% versus 3.1% in SPORTIF V). This is a RRR of 26% (95% CI: 4% to 44%), and ARR of 0.8% during the entire follow-up period (95% CI: 0.1 to 1.6%, P=0.03). There was no statistical evidence of heterogeneity between the trials for major bleeding (P=0.63).

Ximelagatran was associated with significantly less major bleeding than warfarin despite the fact that anticoagulation was carefully monitored and adjusted among patients receiving warfarin, and anticoagulation intensity was not monitored or regulated in patients receiving ximelagatran. However, the absolute rates of bleeding in both treatment groups may be underestimates of those encountered in general practice. This is because most patients enrolled in SPORTIF III and V had preserved renal function and had already been receiving anticoagulant medication for chronic AF. Individuals who were not considered suitable for anticoagulation or who had not tolerated anticoagulation previously were not enrolled.

Ximelagatran was notably associated with a significant excess of elevated liver alanine-aminotransferase (ALT) enzymes compared with warfarin (pooled data: 6.1% versus 0.8%; P<0.0001). It typically occurred 2 to 6 months after initiation of ximelagatran, and was asymptomatic, transient (returning to baseline spontaneously or after cessation of treatment), and without sequelae.

**Implications of the Results of the SPORTIF Trials for Clinicians**

The results of the SPORTIF III and V trials suggest that ximelagatran will become the anticoagulant of choice for patients with atrial fibrillation.

The advantages of ximelagatran are that it reduces the risk of major bleeding compared with warfarin and can be administered orally with a rapid onset of action. It has a predictable pharmacokinetic profile (uninfluenced by the patient’s age, sex, weight, ethnicity, or food intake), and therefore it is not necessary to adjust the dose (except for patients with renal dysfunction in whom a decrease in dose or longer dosing interval is likely to be required) or monitor anticoagulation activity. Furthermore, ximelagatran has a wider therapeutic margin than warfarin and a low potential for food and drug interactions.

The disadvantages of ximelagatran are the need for twice-daily administration, excess occurrence of adverse hepatic effects in 6% of patients (thus potentially requiring monitoring of liver function for up to 6 months after treatment initiation), and the need to estimate creatinine clearance.

### Primary Efficacy and Safety Outcomes for SPORTIF III and V

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>SPORTIF III (n=3407)</th>
<th>SPORTIF V (n=3922)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ximelagatran, (N=1704) n (%)</td>
<td>Warfarin, (N=1703) n (%)</td>
</tr>
<tr>
<td>Stroke or systemic embolism</td>
<td>40 (2.3)</td>
<td>56 (3.3)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>29 (1.7)</td>
<td>41 (2.4)</td>
</tr>
<tr>
<td>ALT &gt;3 times upper limit of normal</td>
<td>107 (6.3)</td>
<td>14 (0.8)</td>
</tr>
</tbody>
</table>

ALT denotes alanine transaminase.
(because ximelagatran is primarily eliminated by the kidneys and data in patients with renal dysfunction are limited). In addition, the cost of ximelagatran for the patient and community is likely to be higher than warfarin.

Ximelagatran is most likely to be prescribed for high-risk patients in AF who can afford it, and who are infrequently prescribed warfarin, such as older (eg, >80 years) patients, those with liver disease (although ximelagatran may also have adverse hepatic effects), and those known to have a common polymorphism for the gene encoding the hepatic microsomal enzyme CYP2C9\textsuperscript{10} and mutations at ALA-10 in the factor IX propeptide.\textsuperscript{11}

Implications of the Results of the SPORTIF Trials for Researchers
The implications of the results of the SPORTIF III and V trials for researchers are 4-fold:

1. To determine the long-term safety of exposure to ximelagatran, particularly regarding liver function.

2. To continue to evaluate the relative safety and effectiveness of other antithrombotic strategies for preventing stroke and systemic embolism in patients with AF. The Atrial fibrillation trial of Monitored, Adjusted Dose vitamin K antagonist, comparing Efficacy and safety with Unadjusted SanOrg 34006/draparinux (MAADEUS) study is a multicenter, randomized, open-label, assessor-blind trial that aims to determine whether once-weekly subcutaneous idraparinux (SanOrg34006, an inhibitor of activated factor X [Xa]) is not inferior to adjusted-dose oral vitamin K antagonists. The Atrial fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE) trial aims to determine whether the combination of clopidogrel 75 mg/d plus aspirin 75 to 100 mg/d is not inferior to adjusted-dose oral vitamin K antagonist among patients who are suitable for anticoagulation (ACTIVE W) and whether the combination of clopidogrel plus aspirin is superior to aspirin among patients who are not suitable for anticoagulation (ACTIVE A).

3. To identify the “gold standard” antithrombotic agent for preventing stroke among patients in AF.

4. To consider whether the combination of ximelagatran and aspirin may be more effective than current antiplatelet regimen in preventing serious vascular events among patients with atherosclerotic transient ischemic attack and ischemic stroke. This hypothesis is fueled by the recent finding that the combination of ximelagatran and aspirin was more effective than aspirin alone in reducing death, nonfatal myocardial infarction (MI), and severe recurrent ischemic events among patients with recent MI.\textsuperscript{22} However, safety will also be an important issue because the addition of ximelagatran to aspirin was associated with a doubling of bleeding complications among patients after MI,\textsuperscript{22} and an increase in bleeding complications in SPORTIF III.\textsuperscript{19}

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References


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