Emerging Therapies

Direct Thrombin Inhibition
A Novel Approach to Stroke Prevention in Patients With Atrial Fibrillation

Mitchell S.V. Elkind, MD, MS; Ralph L. Sacco, MD, MS

Atrial fibrillation (AF) is the most common cause of cardioembolic ischemic stroke, particularly in the elderly, in whom it accounts for as many as 24% of strokes. As the population ages, it is anticipated that the number of strokes caused by AF will increase. Anticoagulant therapy with coumarin derivatives (primarily warfarin) is considered the optimal strategy to reduce the risk of stroke in patients with AF. Warfarin inhibits the vitamin K-dependent post-translational modification of certain coagulation factors (factors II, VII, IX, and X, as well as the anticoagulant factors protein C and protein S) in the liver. This leads to a reduction in generation of thrombin, which is the final rate-limiting step in the coagulation cascade. Thrombin, a serine protease, cleaves fibrinopeptides from soluble fibrinogen to form insoluble fibrin, leading to thrombus formation.

Most trials of anticoagulant therapy in AF have tested the role of warfarin in primary prevention, with relative risk reductions for stroke ranging from 56% to 86% compared with placebo and a pooled risk reduction of 68% (95% confidence interval [CI] 50% to 79%). Warfarin is superior to aspirin, particularly in higher-risk patients with AF. A recent meta-analysis using individual patient data found that warfarin significantly reduced the risk of the combination of hemorrhagic and ischemic strokes compared with aspirin (hazard ratio of warfarin 0.55, 95% CI 0.43 to 0.71). The benefit was seen in all patient groups, but the absolute risk reductions were greatest in those at highest risk, including those over age 75. Aspirin may be sufficiently effective in those at an absolute low annual risk of stroke (ie, <2% per year) but not in patients at higher risk. Overall, warfarin was associated with a modest increase in risk of major hemorrhagic complications compared with aspirin, although this was not seen in each individual trial. There were 2.2 major bleeding events per 100 patient-years of follow up for patients on warfarin versus 1.3 for patients on aspirin.

The European Atrial Fibrillation Trial is the only study that specifically tested the use of anticoagulants in secondary prevention of stroke in patients with AF. Warfarin (International Normalized Ratio [INR] goal 2.5 to 4.0) significantly reduced the risk of recurrent stroke to a degree consistent with that observed in studies of primary prevention (4% on warfarin versus 12% on placebo; 66% relative risk reduction [RRR]; P < 0.001). When compared with 300 mg of aspirin daily, warfarin significantly reduced the risk of recurrent stroke (62% RRR; P < 0.001).

Despite the existence of this grade A evidence and numerous guidelines recommending warfarin for patients with AF at high risk of stroke, warfarin remains underutilized. The reasons for this underuse are manifold. Warfarin is associated with an increased risk of hemorrhage, both extracranial and intracranial, particularly in the elderly and those with other risk factors for bleeding. Dose-response in individuals is unpredictable, the onset of action is slow, and patients may remain subtherapeutic even when coagulation studies are elevated. Warfarin thus entails frequent blood tests for monitoring of therapy and consequent dosage adjustment. Warfarin also has interactions with many other medications and foods, which increase the frequency of monitoring. The risk of teratogenicity in the first trimester may also limit the utility of warfarin in young women. For all these reasons, clinicians may be reluctant to prescribe warfarin to many patients despite its proven efficacy in clinical trials. Thus, there has been a perceived need for an alternative antithrombotic agent for patients with AF.

Direct thrombin inhibitors (DTIs) provide a potential novel approach to preventing thrombosis by inhibiting thrombin at its active site, preventing formation of fibrin and activation of other coagulation factors. Several parenteral DTIs, such as hirudin and argatroban, have been tested and marketed for different acute indications, including deep venous thrombosis and coronary procedures. However, oral DTIs suitable for long-term administration in secondary prevention have only recently become available for clinical testing. The oral DTI that has undergone the most extensive clinical testing thus far is ximelagatran, an oral prodrug that is metabolized to its active form, melagatran, after gastrointestinal absorption. It is a potent and selective inhibitor of thrombin. Its clearance is primarily renal, and it has no clinically relevant interactions with food or with drugs that are metabolized via the cyto-
Ximelagatran has been studied in patients with AF in 2 large randomized controlled trials, the stroke prevention using oral thrombin inhibition in AF (SPORTIF) trials. The first of these, SPORTIF III, was published in *Lancet* in 2003; the results of the second study, SPORTIF V, were presented at national meetings in 2003 but have not yet been published. (SPORTIF I, II, and IV were previous dose-finding and follow-up studies in smaller numbers of patients). These studies were funded by AstraZeneca.

SPORTIF III was an open-label, randomized, multicenter, noninferiority trial of warfarin versus ximelagatran in patients with atrial fibrillation and at least 1 additional risk factor (ie, increased risk of stroke). Additional risk factors required for inclusion were at least 1 of the following: hypertension, aged 75 or older, history of previous stroke, transient ischemic attack (TIA), or systemic embolism, significant left ventricular dysfunction, or aged 65 or younger in combination with either coronary artery disease or diabetes mellitus. There was no upper age limit. Patients were randomized to a fixed dose of oral ximelagatran (36 mg twice daily) or to dose-adjusted warfarin to maintain the INR between 2 and 3. INR was measured at least monthly. Concomitant treatment with up to 100 mg of aspirin daily was permitted. Although treatment was not blinded, outcome events were assessed by local neurologists blinded to treatment.

The primary outcome was ischemic or hemorrhagic stroke or systemic embolism. Importantly, the study was designed to test for noninferiority of ximelagatran. Thus, the null hypothesis was that the primary outcome event rates for patients on ximelagatran would be either the same or lower than for those on warfarin, with an absolute difference of not >2% per year in event rates. Thus, the null hypothesis would be rejected only if event rates for patients on ximelagatran were >2% greater than for patients on warfarin. Secondary end points were (1) major and minor bleeding; (2) treatment discontinuation; (3) ischemic stroke, TIA, or systemic embolism; and (4) death, all stroke, systemic embolism, and acute myocardial infarction.

The study population consisted of 3407 randomized patients in the intention-to-treat analysis, 1704 in the ximelagatran group, and 1703 in the warfarin group. Approximately 70% of patients were men, and the mean age was 70 years. The population was, by design, a high-risk group: 72% were hypertensive, 34% had left ventricular dysfunction, and 24% had a previous history of stroke or TIA.

The annual event rates for the primary outcome were 2.3% in the warfarin group versus 1.6% in the ximelagatran group. The absolute risk reduction was not statistically significant (0.7% per year, 95% CI −0.1 to 1.4), indicating noninferiority of ximelagatran. Results were similar for on-treatment analyses of the secondary efficacy end points (Table 1).

Overall mortality per year was identical in the 2 arms (3.2%); the annual rate of major and or minor bleeding was 1% in ximelagatran and warfarin groups, respectively. Therefore, ximelagatran was noninferior for the primary safety end point as well. There was a statistically significant increase in proportion of patients with elevations in liver alanine aminotransferase (ALT) levels higher than 3× the upper limit of normal on ximelagatran (6% versus 1%; *P*<0.0001). These occurred primarily within 2 to 6 months of treatment and resolved spontaneously in most patients or after stopping therapy. These were generally considered asymptomatic. In 4 patients who developed jaundice, alternative explanations were identified.

Adherence to treatment assignment was good in both arms. The mean INR throughout the study was 2.5 for all measure-
ments among patients assigned to warfarin, and adherence to ximelagatran was 94% based on pill counts. Notably, there was a significantly higher proportion of patients in the ximelagatran arm also taking aspirin during the trial compared with those in the warfarin arm (20% versus 17%; P=0.042). Patients on ximelagatran were also significantly more likely to stop treatment (18% versus 14%; P=0.003), primarily because of elevation in liver transaminases.

SPORTIF III had several limitations. First, the study used an open-label design. Although events were adjudicated locally by event assessors blinded to treatment status, no data were provided regarding the effectiveness of this blinding. Second, the event rates for both treatment arms were somewhat lower than would be expected based on the results of previous trials of warfarin in stroke prevention. Third, the concomitant use of aspirin was significantly higher among those on ximelagatran than those on warfarin. Also, generalization of the results of SPORTIF III must be done cautiously because many of the patients in this clinical trial population may have been less likely to experience adverse events than patients in general practice.

The results of the SPORTIF V trial have not yet been published but were presented at the Scientific Sessions of the American Heart Association in Orlando, Fla, in November 2003.13 SPORTIF V had a similar design to SPORTIF III but differed in at least 1 important way: treatment was double-blinded. Also, SPORTIF V was conducted in 409 centers in the United States and Canada, whereas SPORTIF III was conducted in 23 countries in Europe, Asia, Australia, and New Zealand. The investigators randomized 3922 patients, with a mean treatment duration of 20 months. The primary outcome (stroke or systemic embolism) was not statistically different between the 2 treatment arms: annual rates of 1.6% and 1.2% among those on ximelagatran and warfarin, respectively. Major bleeding did not differ between the 2 groups either (2.4% and 3.1% per year for ximelagatran and warfarin, respectively; P=0.16), but the combination of major and minor bleeding was increased on warfarin (37% and 47% per year for ximelagatran and warfarin, respectively; P<0.0001).

Elevations in ALT occurred 6 times more frequently in patients on ximelagatran, consistent with SPORTIF III. The final publication of the SPORTIF V results are awaited with interest, but the preliminary results in both terms of efficacy and safety appear consistent with SPORTIF III. Moreover, SPORTIF V should serve to further strengthen the conclusions drawn from SPORTIF III because of the presence of double blinding and the extension of the data to a different population of patients (ie, North America).

Therefore, the SPORTIF trials demonstrate that the novel oral antithrombotic agent ximelagatran is as efficacious or more so than warfarin in the prevention of stroke and ischemic events in high-risk patients with AF. However, on the basis of the prespecified noninferiority design of the trials, no claim can be made that ximelagatran is more efficacious than warfarin. In a post hoc analysis of net benefit in SPORTIF III, accounting for outcomes of death, primary ischemic events, and major bleeding, there was a 1.5% statistically significant reduction in the absolute rate of events on ximelagatran (from 6.1% to 4.6% per year) compared with warfarin. However, this type of post hoc analysis must be interpreted cautiously, and the absolute benefit over warfarin, if any, must be considered modest.

Ximelagatran is not currently approved by the Food and Drug Administration. Decisions to use ximelagatran or warfarin will likely be based on considerations beyond efficacy alone (Table 2). Advantages of ximelagatran include its decreased risk of minor bleeding and relative ease of use, with uniform dosing and no need for dose adjustment based

### Table 2. Comparison of Warfarin and Ximelagatran

<table>
<thead>
<tr>
<th><strong>Mechanism of Action</strong></th>
<th>Warfarin</th>
<th>Ximelagatran</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin K antagonist</td>
<td>Decreased thrombin generation</td>
<td>Decreased thrombin activity</td>
</tr>
<tr>
<td><strong>Route of Administration</strong></td>
<td>Oral</td>
<td>Oral</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>Variable</td>
<td>Fixed (36 mg twice daily)</td>
</tr>
<tr>
<td><strong>Pharmacodynamic Properties</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major clearance mechanism</td>
<td>Hepatic</td>
<td>Renal</td>
</tr>
<tr>
<td>Cytochrome P450 interaction</td>
<td>Yes</td>
<td>None</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>~40 hours</td>
<td>240 minutes</td>
</tr>
<tr>
<td><strong>Blood monitoring</strong></td>
<td>Frequent</td>
<td>None</td>
</tr>
<tr>
<td><strong>AF populations tested</strong></td>
<td>All (see text)</td>
<td>AF and ≥1 other risk factor (“high risk”)</td>
</tr>
<tr>
<td><strong>Efficacy in ‘high-risk’ patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compared to placebo</td>
<td>Superior</td>
<td>Not tested</td>
</tr>
<tr>
<td>Compared to aspirin</td>
<td>Superior</td>
<td>Not tested</td>
</tr>
<tr>
<td>Compared to warfarin</td>
<td>—</td>
<td>Noninferior (see text)</td>
</tr>
<tr>
<td><strong>Major Risks</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major hemorrhage</td>
<td>~1–2% annually</td>
<td>~1–2% annually</td>
</tr>
<tr>
<td>ALT elevations</td>
<td>~1%</td>
<td>~6%</td>
</tr>
<tr>
<td>Available as generic</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>Inexpensive</td>
<td>Unknown</td>
</tr>
</tbody>
</table>
on blood levels. The disadvantage to ximelagatran is primarily the 6-fold increase in risk of elevations in ALT. This concern may prompt frequent blood tests anyway, as are needed for warfarin, but it is unlikely that this blood monitoring will need to continue indefinitely or occur as frequently as it must for patients on warfarin. Moreover, ALT elevations were generally asymptomatic and returned to normal either spontaneously or after stopping therapy. However, caution will be prudent in introducing ximelagatran to a large unselected population of patients in whom liver dysfunction may be more likely or more severe. In particular, it should be remembered that renal insufficiency and persistent elevations in liver enzymes were among exclusion criteria for the studies. Furthermore, the relative cost benefit of using ximelagatran remains unknown. Although there is much to be learned about the DTIs, it is likely that ximelagatran and similar drugs will become an important part of the armamentarium against stroke in patients with AF in the future.

References


Key Words: atrial fibrillation ■ cerebral embolism ■ direct thrombin inhibitor ■ stroke prevention ■ ximelagatran
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