Direct Thrombin Inhibition and Stroke Prevention in Elderly Patients With Atrial Fibrillation
Experience From the SPORTIF III and V Trials

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Background and Purpose—Warfarin prevents stroke in atrial fibrillation (AF); however, concerns regarding international normalized ratio control and hemorrhage limit its use in the elderly. The oral direct thrombin inhibitors (DTIs) are potential alternatives to warfarin, offering fixed dosing without drug and dietary interactions and the need for international normalized ratio monitoring. Although ximelagatran, a DTI studied in the Stroke Prevention using an ORal Thrombin Inhibitor in atrial Fibrillation trials, has been withdrawn, development of other DTIs continues. We report our experience in elderly high-risk AF patients on ximelagatran compared with warfarin therapy.

Methods—Data from patients with AF and stroke risk factors randomized in Stroke Prevention using an ORal Thrombin Inhibitor in atrial Fibrillation III and V trials to ximelagatran or warfarin were analyzed for stroke/systemic emboli, bleeding, and raised alanine aminotransferase levels in those ≥75 (n = 2804) and <75 (n = 4525) years.

Results—Ximelagatran was as effective as warfarin in reducing stroke/systemic emboli in the elderly (2.23%/y with ximelagatran vs 2.27%/y with warfarin) as in younger patients (1.25%/y vs 1.28%/y). Total bleeds were significantly lower with ximelagatran compared with warfarin in elderly (40% vs 45%, P = 0.01) and younger (27% vs 35%, P < 0.001) patients. Raised alanine aminotransferase values (>3-fold elevation) among ximelagatran patients were more common in older (7.5% old vs 5.3% young) patients, particularly women (9.5% elderly women vs 6.1% elderly men).

Conclusions—In high-risk elderly AF patients, ximelagatran is as effective as warfarin with less bleeding, but alanine aminotransferase elevations are common, particularly in elderly women. Oral DTIs for stroke prevention show promise in elderly patients. (Stroke. 2007;38;2965-2971.)

Key Words: atrial fibrillation ■ elderly ■ direct thrombin inhibitors ■ stroke ■ ximelagatran

The prevalence of atrial fibrillation (AF) is highly age related and is a major cause of stroke and premature death and disability. The risk of stroke and systemic thromboembolism is highest in the elderly, particularly older women. Anticoagulation with warfarin is effective in reducing the risk of ischemic stroke, but its use is associated with the risk of bleeding; dietary, drug, and genetic polymorphism interactions; and the requirement for frequent monitoring. These problems are particularly important in the elderly because of their increased sensitivity to warfarin, polyparmacy, and comorbidities, all of which may also make monitoring and maintaining a stable international normalized ratio (INR) difficult and increase the risk of bleeding. As a result of these difficulties and the lack of an alternative orally available anticoagulant, elderly patients are often not anticoagulated and remain at high risk of stroke.

The oral direct thrombin inhibitor (DTI) ximelagatran was developed as a potential alternative to warfarin. Ximelagatran, the first oral DTI investigated in large phase III studies, the Stroke Prevention using an ORal Thrombin Inhibitor in atrial Fibrillation (SPORTIF) III and V trials, was found to be as effective as warfarin in preventing stroke in AF. However, owing to concerns regarding the risk of severe hepatotoxicity, ximelagatran was withdrawn from further development in 2006. Nonetheless, other drugs in this class are in development, and data regarding the efficacy and safety of the only oral DTI studied in large clinical trials remain relevant to the development of other oral DTIs and understanding their potential for toxicity.
Elderly patients have not only the highest burden of stroke risk with AF but also the greatest susceptibility to adverse drug effects; therefore, the risk/benefit consideration of therapy is a key issue for older patients. Thus, the purpose of the present study was to determine in elderly patients (≥75 years old) the efficacy and complications of long-term dosing with an oral DTI, ximelagatran, compared with warfarin in the prevention of stroke and systemic embolism (SE) in a pooled analysis of the SPORTIF III and V trials.

**Subjects and Methods**

The rationale, design, and outcomes of SPORTIF III (open label, n=3407) and V (double-blind, n=3922) trials, which compared the efficacy and safety of ximelagatran versus warfarin in patients with nonvalvular AF at risk of ischemic stroke, have been described elsewhere. Both were randomized, multicenter, parallel-group trials, with a duration of treatment of up to 25 months (4941 patient-years of exposure) in SPORTIF III and 31 months (6405 patient-years) in SPORTIF V.

**Patients**

Patients had nonvalvular AF and 1 or more of the following risk factors: hypertension; age 75 years or older; previous stroke, transient ischemic attack, or SE; left ventricular dysfunction; or age 65 years or older with coronary artery disease or diabetes mellitus. Major exclusion criteria were mitral stenosis; previous valvular surgery; AF caused by reversible conditions; severe renal insufficiency (calculated creatinine clearance <30 mL/min); active liver disease or serum liver enzyme levels more than twice the upper normal limit; and conditions associated with increased bleeding risk. Detailed inclusion and exclusion criteria have been described elsewhere. Concomitant antithrombotic drugs, apart from aspirin therapy (100 mg/d or less), were prohibited. Written, informed consent was obtained from all patients according to a protocol approved by local ethics committees.

**Treatment Allocation**

Patients were randomized to treatment with either a fixed dose of ximelagatran (36 mg twice daily) or dose-adjusted warfarin to maintain the INR between 2.0 and 3.0. In SPORTIF III, anticoagulants were administered in an open-label fashion. In SPORTIF V, anticoagulants were administered in a double-blind design with sham INR monitoring and dose adjustment for patients allocated to ximelagatran and warfarin placebo. For all patients, warfarin and placebo doses were adjusted according to local clinical practice, with INR measurements taken at least every 4 weeks. Treatment allocation was balanced according to aspirin therapy at entry, previous stroke or transient ischemic attack, and country according to an adaptive allocation algorithm.

**End Points and Assessments**

Patients were reviewed at 1, 4, and 6 weeks; 2, 3, 4, 5, 6, 8, and 12 months; and every 3 months thereafter for detection of primary end points (stroke [ischemic or hemorrhagic] and SE), transient ischemic attack, acute myocardial infarction, or bleeding complications. A standard stroke-symptom questionnaire was used to enhance primary event detection. A positive response prompted additional evaluation by local study-affiliated neurologists or stroke specialists blinded to treatment, performed as early after symptom onset as possible, and event diagnosis based on clinical findings and the result of brain computed tomography or magnetic resonance imaging. An independent, blinded, central event adjudication committee then reviewed the reports. Bleeding was categorized as major when associated with a functional deficit, decline in hemoglobin of 20 g/L or greater, transfusion, or involvement of an important anatomic site (intracranial, intraspinal, intracerebral, retroperitoneal, pericardial, and atraumatic intra-articular hemorrhage). All other bleeding episodes not meeting the criteria for major bleeds were categorized as minor, even when they resulted in treatment cessation.

**Liver Function Test Monitoring**

Serum concentrations of hepatic transaminases, alkaline phosphatase, and bilirubin were measured monthly for the first 6 months, every 2 months during year 1, and every 3 months thereafter. When any liver function test increased beyond 3 times the upper limit of normal, serum testing was undertaken once weekly until values returned to baseline or normal concentrations, or an alternative cause of the abnormalities was found. Study treatment was discontinued when indices of liver function rose above 5 times the upper limit of normal, when a rise of between 3 and 5 times the upper limit of normal persisted for 8 weeks, or when clinical signs of hepatotoxicity developed.

**Statistical Analyses**

The primary analysis compared treatment efficacy for the first occurrence of stroke or SE event among patients from both trials according to the intention to treat. The proportion of patients having primary events per year and the associated 95% CIs for the difference between treatments were estimated. For the full study populations, the objective was to establish whether ximelagatran was noninferior to warfarin based on a predefined criterion of an absolute margin of 2%/y for the difference in rates of primary events. For this study, the objective was to exploratively compare efficacy (prevention of stroke/SE) and safety (bleeding and alanine aminotransferase [ALT] elevations) results between treatments in patients ≥75 years versus in patients <75 years and correspondingly, among elderly patients by sex. Event rate calculations assumed a constant event rate over time, with the exception of ALT elevations, for which all analyses were based on patients rather than patient-years as analysis units. Reported probability values resulted from Fisher’s exact test (2 sided). A value of P<0.05 was considered statistically significant. No corrections for multiple testing have been made. All patients were followed up for primary events and mortality until study close; remaining end points, including bleeding, were recorded during the on-treatment period. Hence, bleeding was analyzed with an on-treatment approach. All analyses were performed with individual patient data after pooling of the study databases.

**Results**

**Patients**

The outcomes of the 8460 enrolled and 7332 (3 later withdrew) randomized participants during the course of both trials have been previously described. Clinical characteristics by age of the remaining 7329 randomized patients are summarized in Table 1. Two thousand eight hundred four subjects (38%) were ≥75 years, the median age being 72 years, and 1670 (60%) were male. The median number of risk factors was 3 in those ≥75 years and 2 in those <75 years. Total patient follow-up for the combined trials was 11 346 patient-years at risk. The mean±SD duration of follow-up was 18.5±4.8 months. Patients ≥75 years were treated for an average of 18.3 months (4321 patient-years). Patients <75 years were treated for an average of 18.5 months (7025 patient-years).

**Clinical Characteristics by Sex in Older Patients**

For patients 75 years and older, the mean age was 78 years in men and 79 years in women. The median number of risk factors in older men and women was 3. Sixty-eight percent (n=1129) of older men and 77% (n=873) of older women had a history of hypertension, and the mean systolic blood pressure at entry into the study was 135.0 mm Hg in older
men and 139.8 mm Hg in older women. Coronary artery disease was present in 52% (n = 865) of men and 40% (n = 456) of women. Twenty-two percent (n = 373) of older men and 19% (n = 218) of older women were on concomitant aspirin therapy (100 mg/d). There were no differences across treatment groups for these characteristics.

**INR Values**
Details of patient withdrawals and times in the therapeutic range with warfarin treatment have been previously reported.10 In patients assigned to warfarin, the mean (SD) INR was 2.43 (0.67) across all measurements during the course of the study. Time within the therapeutic range of 2.0 to 3.0 did not differ between patients <75 years (67.4%) and patients ≥75 years (67.9%) or between older men (69.3%) and older women (66.0%). Overanticoagulation (INR >3.2) and subtherapeutic anticoagulation (INR <1.8) occurred in 8.1% and 9.4%, respectively, of the follow-up duration, with excessive anticoagulation (INR >5.0) occurring 0.4% of the time.

**Treatment Efficacy on Stroke and SE**
**Effects of Age**
Stroke and SE events were more common in patients ≥75 years compared with patients <75 years (2.25%/y versus 1.26%/y, P<0.0001). Figure 1a shows the cumulative proportion of patients who experienced primary end points over 24 months according to the intention to treat in each age group. In older patients, the primary event rate was 2.23%/y (95% CI, 1.60 to 2.86) with ximelagatran compared with 2.27%/y (95% CI, 1.63 to 2.91) with warfarin (difference = −0.04%/y; 95% CI, −0.94 to 0.86; P=1.00). In younger patients, the primary event rate was 1.25%/y (95% CI, 0.87 to 1.62) with ximelagatran compared with 1.28%/y (95% CI, 0.91 to 1.66) with warfarin (difference = −0.04%/y; 95% CI, −0.56 to 0.49; P=0.92). The noninferiority criterion of the difference in primary event rates per year was fulfilled for both elderly and younger patients.

**Effects of Sex in Older Patients**
Stroke and SE events occurred at a rate of 2.01%/y in older men and 2.61%/y in older women. Figure 1b shows the cumulative proportion of patients by sex in the older age group who experienced primary end points over the 24 months according to an intention-to-treat analysis. The primary event rate in elderly men was 1.70%/y with ximelagatran versus 2.33%/y with warfarin (difference = −0.63%/y; 95% CI, −1.74 to 0.47; P=0.26) and in elderly women, 3.04%/y with ximelagatran compared with 2.19%/y with

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**Table 1. Characteristics of Randomized Patients by Age**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ximelagatran</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;75 Years</td>
<td>≥75 Years</td>
</tr>
<tr>
<td>Male</td>
<td>1670 (74%)</td>
<td>853 (60%)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>65.7 (7.2)</td>
<td>79.3 (3.6)</td>
</tr>
<tr>
<td>Body weight, mean (SD), kg</td>
<td>90.8 (21.2)</td>
<td>77.7 (15.6)</td>
</tr>
<tr>
<td>White</td>
<td>2013 (90%)</td>
<td>1336 (96%)</td>
</tr>
<tr>
<td>Black</td>
<td>52 (2%)</td>
<td>15 (1%)</td>
</tr>
<tr>
<td>Asian</td>
<td>169 (8%)</td>
<td>47 (3%)</td>
</tr>
<tr>
<td>Oriental</td>
<td>11 (0%)</td>
<td>1 (0%)</td>
</tr>
<tr>
<td>Aspirin use at entry</td>
<td>408 (18%)</td>
<td>289 (20%)</td>
</tr>
<tr>
<td>VKA before randomization</td>
<td>1801 (80%)</td>
<td>1082 (76%)</td>
</tr>
<tr>
<td>Systolic blood pressure, mean (SD), mm Hg</td>
<td>134.6 (17.7)</td>
<td>137.2 (18.5)</td>
</tr>
<tr>
<td>AF onset &lt;1 year</td>
<td>410 (18%)</td>
<td>288 (20%)</td>
</tr>
<tr>
<td>Paroxysmal AF</td>
<td>286 (13%)</td>
<td>156 (11%)</td>
</tr>
<tr>
<td>One risk factor</td>
<td>887 (40%)</td>
<td>111 (8%)</td>
</tr>
<tr>
<td>Two risk factors</td>
<td>830 (37%)</td>
<td>382 (27%)</td>
</tr>
<tr>
<td>Three or more risk factors</td>
<td>520 (23%)</td>
<td>926 (65%)</td>
</tr>
<tr>
<td>Previous stroke or transient ischemic attack</td>
<td>438 (20%)</td>
<td>348 (25%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1799 (80%)</td>
<td>1014 (71%)</td>
</tr>
<tr>
<td>Previous non–central nervous system embolism</td>
<td>97 (4%)</td>
<td>69 (5%)</td>
</tr>
<tr>
<td>Left ventricular dysfunction</td>
<td>835 (37%)</td>
<td>474 (33%)</td>
</tr>
<tr>
<td>Age 65 years or older and coronary artery disease</td>
<td>728 (32%)</td>
<td>675 (48%)</td>
</tr>
<tr>
<td>Age 65 years or older and diabetes</td>
<td>390 (17%)</td>
<td>287 (20%)</td>
</tr>
</tbody>
</table>

VKA indicates vitamin K antagonists.

Characteristics are of randomized patients: ximelagatran, n = 3664; warfarin, n = 3665; <75 years, n = 4525; ≥75 years, n = 2804; from combined SPORTIF III and V trials.
warfarin (difference = 0.85%/y; 95% CI, −0.68 to 2.37; \(P=0.29\)).

Hemorrhagic Stroke and Bleeding Events

**Effects of Age**

Eleven hemorrhagic strokes (5 in the ximelagatran group and 6 in the warfarin group) occurred in patients ≥75 years (0.25%/y), and 6 hemorrhagic strokes (1 with ximelagatran and 5 with warfarin) occurred in patients <75 years (0.09%/y). Patients on ximelagatran therapy had fewer major bleeds compared with those on warfarin therapy (Figure 2a) in both age groups, but this difference did not reach statistical significance (difference = −0.9; 95% CI, −2.0 to 0.2; \(P=0.13\) in older patients and difference = −0.4; 95% CI, −1.0 to 0.2; \(P=0.2\) in younger patients). Rates of combined major and minor bleeds in elderly patients were significantly less with ximelagatran (39.9%/y; 95% CI, 36.6 to 43.3) compared with warfarin (44.7%/y; 95% CI, 41.1 to 48.2; difference = −4.8%/y; 95% CI, −9.4 to −0.2; \(P=0.014\)). In younger patients, combined major and minor bleeds were also significantly less with ximelagatran (27.2%/y; 95% CI, 25.1 to 29.2) compared with warfarin (35.5%/y; 95% CI, 33.1 to 37.8; difference = −8.3%/y; 95% CI, −11.4 to −5.1; \(P<0.001\)).

**Effects of Sex in Older Patients**

Older men had significantly fewer major bleeds with ximelagatran than with warfarin (difference = −1.79; 95% CI, −3.32 to −0.25; \(P=0.02\); Figure 2b), but this trend was not seen in older women (difference = 3.4, 95% CI, −1.3 to 2.1; \(P=0.75\)). In both older men and older women, combined bleeding rates were less with ximelagatran, but this difference was not statistically significant: in elderly men 39.7%/y (95% CI, 35.3 to 43.9) with ximelagatran versus 43.5%/y (95% CI, 38.9 to 48.1) with warfarin (\(P=0.12\)); in elderly women 40.4%/y (95% CI, 35.0 to 45.8) with ximelagatran versus 46.3%/y (95% CI, 40.6 to 52.0) with warfarin (\(P=0.057\)).

Liver Function Tests

**Effects of Age**

Three- or 5-fold elevations in ALT levels with ximelagatran were significantly more frequent in older patients compared with younger patients (Table 2) and necessitated discontinu-
ation of the study drug in 64 of 106 (60%) elderly patients compared with 64 of 118 (54%) younger patients. No age difference in elevated ALT levels was seen in patients on warfarin therapy.

Effects of Sex in Older Patients
Abnormal ALT values with ximelagatran were also more common in older women compared with older men (9.5% versus 6.1%, \(P<0.018\)), but no sex difference was found for warfarin. Discontinuation of the study drug because of \(\geq 3\)-fold increases in ALT was required in 33 of 52 (63%) older men and in 31 of 54 (57%) older women assigned to ximelagatran and in 1 of 5 older men and 4 of 5 older women assigned to warfarin.

Discussion
In this pooled analysis of 7329 randomized patients from the SPORTIF III and V trials, we have shown that in high-risk elderly patients with nonvalvular AF, the oral DTI ximelagatran is as effective as well-controlled warfarin for the prevention of stroke and systemic thromboembolism. With 2804 elderly patients comprising 4321 patient-years of exposure, the combined SPORTIF trials are the largest and longest-term prospective trials involving high-risk elderly patients using an oral DTI for the prevention of stroke and SE.

Ximelagatran was developed as an alternative to warfarin and, until recently, was in phase III development for thromboembolic indications. However, the drug was withdrawn from further development early in 2006 based on unexpected adverse liver events and the drug’s hepatic profile.\(^8\) Despite this, as the first of its kind to be studied in large and long-term clinical trials, data regarding its efficacy and safety are still valid and relevant to further development of drugs in this class and to an understanding of the potential mechanisms of the hepatotoxicity. This study has shown that the elderly, in particular elderly women, appear to be more susceptible to developing elevated transaminase values, consistent with other studies on adverse drug effects that have demonstrated older women to be most susceptible.\(^\text{11}\) The reasons why older
particularly female patients are at higher risk are unknown, nor is (are) the mechanism(s) of ALT elevation known or whether this is a drug-specific or class effect.

The elderly are a particularly high-risk group for stroke in AF but are also at the highest risk of adverse drug events. Therefore, the balance of risk versus benefit of therapy needs to be specifically addressed in this group of patients. We have shown that anticoagulation with the oral DTI ximelagatran was as effective as warfarin in reducing stroke and SE in high-risk older patients and was associated with less bleeding. The efficacy of warfarin treatment in the SPORTIF III and V trials was achieved with close monitoring of the INR, such that subtherapeutic anticoagulation (INR <1.8) occurred only 9.4% of the time during warfarin therapy. This intensity of INR monitoring is unlikely to be replicated in most clinical settings, and therefore, more events with warfarin treatment would be expected in usual practice, lending further support for the efficacy of ximelagatran compared with warfarin in stroke and SE prevention in this high-risk group. Perhaps surprisingly, we found no difference in time spent in the therapeutic range between younger and older patients. Older patients had fewer total bleeding events with ximelagatran compared with warfarin. The rate of major bleeding was lower in the ximelagatran group compared with the warfarin group, although this difference did not reach statistical significance, except in older men. These exploratory results may be partly related to the greater likelihood of older men having background vascular disease requiring concomitant aspirin. Recently published data have shown that aspirin in combination with warfarin, but not ximelagatran, is associated with more major bleeds compared with either of these agents alone. Nonetheless, this finding warrants a confirmatory study of the increased bleeding complications in older men on warfarin therapy.

The number of major bleeding episodes in this study may have been too small to detect a significant difference in all groups. The low rate of major bleeding events in this and previous randomized trials is in contrast to the incidence in clinical practice and may be related to the intensity of monitoring and follow-up or subject selection. A previous large cohort study found that an INR >5.0 was an independent risk factor for warfarin-associated bleeding, and subsequent studies have shown that in older patients, INR values >3.5 are associated with increased risk of cerebral hemorrhage. In our study, excessive anticoagulation (INR >5) occurred 0.4% of the time on warfarin treatment, with an INR >3.2 occurring 8% of the time. It is plausible that in usual practice, where the INR is often not as carefully monitored, the risk of major bleeding with warfarin would be expected to be higher.

A potential limitation of this pooled analysis is that SPORTIF III was open label, whereas SPORTIF V was double-blind. The study designs were otherwise identical. The open-label design of SPORTIF III could have led to biased event reporting. Differences in primary end points between the trials was found in a previous pooled analysis for patients on warfarin but not on ximelagatran therapy and could have been a reflection of differences in INR monitoring methodology, in global medical practice, or chance. However, no heterogeneity in bleeding rates was found with ximelagatran and warfarin across the pooled studies.

The main clinical implication of this study is that in elderly patients with nonvalvular AF and at high risk of stroke, direct thrombin inhibition by ximelagatran is as effective as well-controlled anticoagulation with warfarin, but the former has less potential for bleeding. This finding suggests that oral DTIs show promise in high-risk elderly patients in whom bleeding complications are of concern, and development of drugs in this class has potential. If safety can be achieved, the oral DTI agents may allow more high-risk patients to be anticoagulated and protected from stroke, patients who might have otherwise been excluded from anticoagulation in the first instance because of the specific concerns related to warfarin. In the United States, >2.5 million individuals have AF and a 5-fold risk of stroke; however, management of warfarin therapy remains challenging and suboptimal. In western Europe, similar numbers are at risk, and maintaining a therapeutic INR is difficult to achieve, even in well-managed centers. Therefore, the potential gains from simplifying anticoagulation management, particularly in the elderly, so that it becomes easier and safer cannot be overstated.

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Disclosures

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References

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