Anticoagulation in women with non-valvular atrial fibrillation in the stroke prevention using an oral thrombin inhibitor (SPORTIF) trials

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KEYWORDS
Atrial fibrillation; Women; Anticoagulation; Thromboembolism

Aims The risk of stroke is greater among women with atrial fibrillation (AF) than men. Warfarin protects against stroke, but treatment-related bleeding occurs more often in women than in men.

Methods and results SPORTIF III (open label, n = 3410) and V (double-blind, n = 3922) included 2257 women with AF and one or more stroke risk factors randomized to warfarin [target international normalized ratio (INR) 2.0–3.0] or ximelagatran (36 mg twice daily). Primary outcomes were all stroke (ischaemic/haemorrhagic) and systemic embolic event. Women were older, on average, than men, 73.4 ± 8.0 vs. 69.8 ± 9.0 years (P < 0.0001). More women were >75-years old and women had more risk factors than men had (P < 0.0001). The INR on warfarin (mean 2.5 ± 0.7) was within target range for 67% of follow-up regardless of gender. Women more often developed primary events [2.0%/year, 95% confidence interval (CI) 1.60–2.56%/year vs. 1.44%/year, 95% CI 1.18–1.71%/year in men; P = 0.016]. Major bleeding rates were similar (P = 0.766) but women experienced more overall (major/minor) bleeding (P < 0.001). Warfarin was associated with more overall bleeding in both genders and more major bleeding in women than in men (P = 0.001).

Conclusion When compared with men with AF, women in these studies were older and had more stroke risk factors. Women were more prone to anticoagulant-related bleeding; the higher rate of thrombo-embolism among women was related to more frequent interruption of anticoagulant therapy.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac rhythm disorder encountered in clinical practice and an important risk factor for ischaemic stroke.2–4 Its prevalence increases with age, affecting women slightly less often than men.2–6 Stroke rates with AF are higher in women than in men3–7–10 and AF is the most common cause of stroke in elderly women.

Despite the established efficacy of anticoagulation for prevention of stroke in both men and women with AF, warfarin is prescribed for less than one-third of women with AF at hospital discharge, a lower rate than for men, and this under-use is associated with adverse outcomes.11 Few randomized trials have enrolled a sufficient proportion of women to specifically evaluate differential efficacy or safety on the basis of gender,12–13 but data from a prospective cohort demonstrate that women have a higher risk than men for AF-related thromboembolism and that warfarin is as effective in women as in men with AF.10

The Stroke Prevention using an Oral Thrombin Inhibitor in patients with AF(SPORTIF) programme included two clinical trials that compared the efficacy and safety of ximelagatran vs. warfarin in patients with AF at risk of ischaemic stroke. The combined cohort of SPORTIF III and V includes the largest number of women yet reported with non-valvular AF followed prospectively on anticoagulation; 50% of the women enrolled were over 75 years of age. The results provide information about sex-based and age-based differences in rates of ischaemic events and bleeding among anticoagulated patients with AF and about the relative safety and efficacy of warfarin and ximelagatran in women and men.

Methods

The design, characteristics of enrolled patients, statistical analysis, and main results of the SPORTIF III and V trials have been
reported. Entry criteria, based on current clinical indications for antithrombotic therapy, were identical for the two studies and included persistent or paroxysmal non-valvular AF verified by ECG within 2 weeks before randomization and at least one of the following additional risk factors for stroke: hypertension, age $\geq 75$ years, previous stroke, transient ischaemic attack (TIA) or systemic embolic event (SEE), left ventricular (LV) dysfunction [LV ejection fraction (LVEF) $< 40\%$ or symptomatic congestive heart failure (CHF)], age $\geq 65$ years with coronary artery disease (CAD), or age $\geq 65$ years and diabetes mellitus. The principal exclusion criteria were: stroke, TIA, or SEE within 30 days before entry; bleeding disorders; conditions requiring conventional anticoagulant therapy; AF secondary to reversible disorders (e.g. thyrotoxicosis); hypertension $> 180/100$ mmHg despite medication; previous disabling stroke with modified Rankin score $> 3$; acute coronary syndrome within 30 days; planned cardioversion, treatment with platelet-inhibitor drugs other than aspirin $\leq 100$ mg/day within 10 days; renal insufficiency (calculated creatinine clearance $< 30$ mL/min); active liver disease or persistent elevation of liver enzymes two or more times the upper limit of normal (ULN); childbearing potential, pregnancy, or lactation.

**Randomized treatment**

Patients were randomized to treatment with ximelagatran at a fixed dose of 36 mg twice daily or to warfarin dose adjusted to maintain the international normalized ratio (INR) between 2.0 and 3.0, based on blood test monitoring at maximum intervals of 4 weeks. Allocation was balanced according to aspirin therapy at entry, previous stroke or TIA, and country, using an adaptive allocation algorithm. In SPORTIF III, treatment was administered open label at 259 sites in 23 countries in Europe, Australia, New Zealand, and Asia, with blinded endpoint event assessment. In SPORTIF V, treatment was double blind at 409 sites in North America.

**Concomitant estrogen replacement therapy**

Some women took estrogen replacement therapy (ERT) during the trial on the advice of their physician. For this analysis, women were considered to be on ERT when either oral or subcutaneous estrogen alone or in conjunction with progesterone therapy was recorded as a concomitant medication at randomization, but topical therapies and progesterone monotherapy were excluded.

**Clinical assessments and endpoints**

After randomization, patients were seen at 1, 4, and 6 weeks and then at 2, 3, 4, 5, 6, 8, 10, and 12 months, and every 3 months thereafter for detection of stroke or SEE (primary events), TIA, acute myocardial infarction (MI), or bleeding complications. Events were also detected by a standard stroke-symptom questionnaire administered by telephone; positive responses prompted additional evaluation. A study-affiliated neurologist or stroke specialist blinded to treatment allocation evaluated all possible primary events and TIA. An independent, central clinical event adjudication committee also blinded to treatment reviewed clinical reports of all primary and secondary events. Primary endpoints for the trial were stroke and SEE. Secondary endpoints were acute MI, TIA, death, and major and minor bleeding.

**Statistical analysis**

The trials were based on establishing non-inferiority within an absolute margin of 2%/year for the difference in primary event rates between the two treatment groups. The analysis reported here was planned to compare the efficacy and safety of anticoagulation in women with that in men enrolled in both trials. Comparisons were made for age $\geq 75$ or younger, paroxysmal or persistent AF, and use of ERT at randomization. In addition, we performed multivariable analysis of the pooled data for trial effect, study treatment effect, and their interactions within these subgroups. Sensitivity analyses comparing men and women for the primary endpoint were performed on the basis of a Cox-regression using study as a factor in the model and for interaction between study and gender.

The intention-to-treat (ITT) analysis for primary events and mortality included all randomized patients until study closure, irrespective of protocol adherence, or continued participation. Remaining endpoints were recorded during the on-treatment (OT) period with exposure censored from the 31st consecutive day or 61st cumulative day off study drug. Events before first dose intake in randomized patients were included in the analysis. No patient was counted more than once for a given composite endpoint.

All patients were followed for primary events and mortality until study censoring. Remaining outcomes were recorded during the OT period. Hence, composite endpoints confined to stroke, SEE, and death were analyzed according to ITT, whereas assessments of all other outcomes, composite endpoints and exploratory analyses used the OT approach.

In addition to analyses of efficacy, the safety profiles of ximelagatran and warfarin were compared between genders. For each treatment group, the proportions of patients experiencing major bleeding, minor bleeding, or bleeding causing permanent treatment cessation were calculated, accounting for duration of exposure for each patient. Other adverse events and laboratory variables were summarized using descriptive statistics.

The analysis of the difference in primary event rates between the treatment groups was made under the assumption of exponentially distributed lifetimes. This is equivalent to assuming a constant event rate over time and hence the probability of an event over a year can be estimated from the complete follow-up of all patients. The variance for the difference in event rates was estimated using the method described by Cox and Oakes. Two-sided $P$-values for differences between treatments were obtained by Fisher's exact test, using the number of patient-years as analyses units. ERT was a predefined subgroup analysis prior to completion of the trials. Because both age $> 75$ and pattern of AF (paroxysmal or persistent) are perceived risk factors for AF, we performed subgroup analyses. Also, for both SPORTIF III and V comparisons of primary event rates according to age $> 75$ vs. $< 75$ was a predefined tertiary endpoint. Thus the writing group felt that examination in this cohort was important for substudy analyses.

Cox-regression analyses used the following baseline stroke risk factors as covariates for multivariable analyses after validation of the proportional hazards model assumption: gender, baseline systolic blood pressure and diastolic blood pressure (DBP), prior stroke/TIA, SEE, hypertension, CAD (MI, angioplasty, or angina), diabetes mellitus, LV dysfunction (LVEF $< 40\%$ or symptomatic CHF), age (both as a continuous and as a categorical variable), smoking (past or present vs. none), body mass index ($< 30$ vs. $\geq 30$), alcohol as a dichotomous variable, trial, and study treatment.

**Results**

**Baseline characteristics**

Baseline characteristics of enrolled patients are compared by gender in Table 1. Of the 7329 subjects enrolled, 2257 (30.8%) were women (30.9% in SPORTIF III and 30.7% in SPORTIF V). The mean age was 73.4 $\pm$ 8 years for women and 69.8 $\pm$ 9 years for men ($P < 0.0001$). The mean blood pressure in women was 138.5 $\pm$ 18 mmHg systolic and 79.8 $\pm$ 10 mmHg diastolic when compared with 134.0 $\pm$ 18 mmHg ($P < 0.0001$) and 79.2 $\pm$ 11 mmHg in men ($P = 0.015$). Ninety-three per cent of women and 92% of men were Caucasian compared to other races ($P < 0.0001$). Only 5% of women were occasional or habitual smokers when compared with 11% of men ($P < 0.0001$). The onset of AF was within 1 year in 23% of women vs. 18% of...
men \( (P < 0.0001) \). A history of hypertension was more frequent (81% vs. 75%; \( P < 0.0001 \)), but the prevalence of diabetes (22% vs. 24%; \( P = 0.03 \)), coronary heart disease (38% vs. 48%; \( P < 0.0001 \)), and LV systolic dysfunction (33% vs. 38%; \( P < 0.0001 \)) was lower among women. Women had a larger number of associated thrombo-embolic risk factors (43% vs. 38% with three or more risk factors in addition to AF; \( P < 0.0001 \)).

Prior to randomization, women were less often treated with cardiovascular medications such as \( \beta \)-blockers, angiotensin-converting enzyme (ACE) inhibitors, or statins but there was no difference in use of vitamin K antagonists or aspirin. After randomization, the INR was within the target range (2.0–3.0) 66.6% of the time on treatment and in the expanded range of 1.8–3.2 for 81.5% of the time among the 1099 women assigned to warfarin therapy. Among men on warfarin \( (n = 2525) \), INR was between 2.0 and 3.0 for 67.8% and between 1.8 and 3.2 for 82.7% of the time on treatment.

### Endpoint events

By ITT analysis, more women than men developed primary events (stroke or SEE), with 72 women experiencing events during 3465 patient-years [2.08%/year, 95% confidence interval (CI) 1.60–2.56%/year] vs. 112 men during 7759...
patient-years (1.44%/year, 95% CI 1.18–1.71%/year; \( P = 0.016 \); Table 2). However, this difference was limited to the ximelagatran group (2.17%/year, 95% CI 1.48–2.87%/year vs. 1.38%/year, 95% CI 1.00–1.75%/year; \( P = 0.03 \)). There was no significant difference in primary event rates based on gender in the warfarin group (Figure 1). Comparing women in the ximelagatran and warfarin groups, 38 patients experienced primary events during 1748 patient-years with ximelagatran (2.17%/year) vs. 34 during 1717 patient-years for warfarin (1.98%/year; \( P = 0.722 \)). Among men, during 3854 patient-years, 53 developed primary events in the ximelagatran group (1.38%/year) when compared with 59 in the warfarin group during 3905 patient-years (1.51%/year; \( P = 0.635 \)).

In contrast to their more favourable outcome with respect to the primary events, men suffered higher all-cause mortality than women, with 301 male deaths over 7831 patient-years (3.84%/year, 95% CI 3.41–4.28%/year) when compared with 93 deaths among women over 3507 patient-years (2.71%/year, 95% CI 2.16–3.25%/year; \( P = 0.002 \)). Furthermore, the difference in primary event rates between women and men was not apparent when assessed by OT analysis (1.61%/year in women, 95% CI 1.16–2.07%/year vs. 1.45%/year in men, 95% CI 1.17–1.73%/year; \( P = 0.53 \)). The mean number of stroke risk factors other than AF among women who discontinued anticoagulation during the trial was 2.54 (95% CI 2.47–2.61) when compared with a mean of 2.21 (95% CI 2.17–2.24), among those who were able to sustain anticoagulation (\( P < 0.0001 \)). Primary events included haemorrhagic stroke in four women (three fatal), ischaemic stroke in 40 (seven fatal), and SEE in five (one fatal). Ten men developed haemorrhagic stroke of which five were fatal, 86 ischaemic stroke (eight fatal), and six SEE (one fatal), using a 30-day rule.

### Bleeding complications

There was no difference in major bleeding complications between women and men overall (2.25% vs. 2.15%/year; \( P = 0.765 \)) or in either of the treatment groups (0.57%/year on ximelagatran, \( P = 0.208 \), and \( 0.35%/year on warfarin, \( P = 0.491 \)). Among women, there was no difference in major bleeding in the ximelagatran vs. warfarin groups. More men developed major bleeding on warfarin (91 events; 2.57%/year) when compared with those on ximelagatran (58 events, 1.71%/year; \( P = 0.016 \)). Combined rates of both major and minor bleeding were greater among women than men (41.29%/year vs. 33.91%/year; \( P = 0.001 \)) that carried across both treatment groups (a difference in rates of 5.37%/year between women and men on ximelagatran, \( P = 0.001 \), and a difference of 8.56%/year on warfarin, \( P < 0.001 \)). Comparing the two treatments, bleeding was less frequent among women in the ximelagatran group (35.48%/year) than in the warfarin group (44.82%/year, \( P < 0.001 \)). The same was true among men (30.85%/year in the ximelagatran group vs. 37.01%/year in the warfarin group; \( P < 0.001 \)).

### Liver function abnormalities

Women in the ximelagatran group developed serum levels of \( S \)-alanine aminotransferase (ALT) beyond three times the ULN more often than men (8.4% vs. 5.1%; \( P < 0.001 \); Table 3). Incidences in the warfarin group were 1.0% among women and 0.7% among men. Incidences of ALT

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### Table 2: Event rates: women vs. men and women aged ≥75 years vs. women aged <75 years

<table>
<thead>
<tr>
<th></th>
<th>Events, ( n )</th>
<th>Patient-years</th>
<th>Event rate, % per year</th>
<th>( P )-value</th>
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<tbody>
<tr>
<td><strong>Stroke and SEE (ITT analysis)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>72</td>
<td>3465</td>
<td>2.08</td>
<td></td>
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<tr>
<td>Men</td>
<td>112</td>
<td>7759</td>
<td>1.44</td>
<td>0.016</td>
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<tr>
<td>Women aged ≥75 years</td>
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<td>1724</td>
<td>2.61</td>
<td>0.032</td>
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<td>27</td>
<td>1742</td>
<td>1.55</td>
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<td><strong>Mortality</strong></td>
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<td></td>
<td></td>
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<tr>
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<td>95</td>
<td>3507</td>
<td>2.71</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>301</td>
<td>7831</td>
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<td>0.002</td>
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<tr>
<td>Women aged ≥75 years</td>
<td>67</td>
<td>1746</td>
<td>3.84</td>
<td></td>
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<tr>
<td>Women aged &lt;75 years</td>
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<td>1760</td>
<td>1.59</td>
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<tr>
<td><strong>Stroke and SEE (OT analysis)</strong></td>
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<td></td>
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<tr>
<td>Women</td>
<td>49</td>
<td>3037</td>
<td>1.61</td>
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<tr>
<td>Men</td>
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<td>6960</td>
<td>1.45</td>
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<tr>
<td><strong>MI</strong></td>
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<tr>
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<tr>
<td>Men</td>
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<td><strong>Major bleeding</strong></td>
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<tr>
<td>Women</td>
<td>68</td>
<td>3022</td>
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<tr>
<td>Men</td>
<td>149</td>
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<tr>
<td>Women aged &lt;75 years</td>
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<tr>
<td><strong>Major and minor bleeding</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Women</td>
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<tr>
<td>Men</td>
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<tr>
<td>Women aged &lt;75 years</td>
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</table>

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beyond five times the ULN occurred more often in women than in men (4.5% vs. 2.6%) on ximelagatran but with little difference on warfarin (0.4% vs. 0.3%).

Differences based on age

Compared with younger women, those aged ≥75 years were more often Caucasian (96 vs. 90%), non-smokers (68 vs. 65%), with higher systolic blood pressure (139.8 vs. 137.2 mmHg), taking aspirin (15 vs. 12%), with persistent AF (89 vs. 85%) and a history of TIA (12 vs. 10%). Elderly women had more risk factors for stroke (three or more in 63 vs. 23%) but less often had a history of hypertension (77 vs. 84%) and had a lower DBP (79.0 vs. 80.7 mmHg) or diabetes (18 vs. 36%). Older women more often had CAD than younger women (40 vs. 29%).

More women over the age of 75 years developed primary events (2.61 vs. 1.55%/year; \( P = 0.032 \); ITT analysis). Older women also displayed greater all-cause mortality \( (P < 0.001; \) ). Rates of major bleeding were not significantly different between older and younger women (2.78 vs. 1.74%; \( P = 0.065 \)), but the elder group developed more overall (and minor) bleeding events (44.73 vs. 38.05%/year; \( P = 0.002 \)). There were no differences in major bleeding based on treatment group assignment among either older women (2.97%/year in the ximelagatran group vs. 2.60%/year in the warfarin group; \( P = 0.752 \)) or younger women (1.66%/year in the ximelagatran group vs. 1.83%/year in the warfarin group; \( P = 0.848 \)).

Differences based on ERT

In both trials combined, 381 women (17%) took ERT at randomization and for more than half the follow-up period, and 413 (18%) used ERT at some point during the trial. Of those taking ERT at entry, 14 developed ischaemic stroke, SEE, or TIA and 27 had ischaemic stroke, SEE, TIA, MI, or death. The small number of women using ERT and the infrequency of events left the results of univariate and multivariable analyses inconclusive.

Differences based on pattern of AF

Most women (87%) had persistent AF. There were no differences in baseline demographics between those with
persistent vs. paroxysmal AF except for age (42% with paroxysmal AF were ≥75 years vs. 52% with persistent AF; \( P = 0.002 \)) and LV dysfunction (25% with paroxysmal AF vs. 34% with persistent AF; \( P = 0.0025 \)). Women with persistent AF had more stroke risk factors (45 vs. 35% with more than three risk factors in addition to AF; \( P < 0.0001 \)).

**Multivariable analyses**

There were no significant interactions between gender and either trial or treatment; hence, data were pooled over trial and treatment for all gender-based analyses. When included as the only variable in the model, gender was significantly related to the primary event rate (hazard ratio (HR) 1.44; 95% CI 1.07–1.93; \( P = 0.0161 \)). After adjusting for the covariates above, however, this difference was no longer significant (HR 1.27; 95% CI 0.91–1.76; \( P = 0.16 \)). On the basis of Cox-regression analyses, the \( \beta \)-value for the gender comparison for the primary endpoint remained unchanged with \( P = 0.016 \) or without \( P = 0.016 \) study present as a factor in the model. There was no interaction between study and gender \( (P = 0.92) \).

**Discussion**

This cohort of 2257 women with AF on anticoagulation is the largest described to date; even so, as only 31% of randomized patients were women, statistical power of conclusions specifically involving women remains limited. Compared with men in these trials, women were typically older than 75 years, had a history of hypertension, and had more risk factors for stroke though they were less often diabetic and had normal LV function. By ITT analysis, women had a higher rate of primary events while there was no difference by OT analysis. Although one interpretation is that the higher rate of thrombo-embolism among women with AF might have been related to interruption of anticoagulant therapy, it was not possible to verify whether the number of primary events following drug interruption differed between genders. The data do, however, support the conclusion that those who discontinued therapy were at higher intrinsic risk, similar to the recent report from the ATRIA investigators.\(^\text{10}\)

Although the SPORTIF III trial was conducted open label and SPORTIF V was double blind, we consider it valid to combine data from both because of the measures taken to minimize bias. The ‘hard’ primary endpoints (all strokes and SEE) and multiple levels of blinded adjudication were the same for both trials. A specific symptom questionnaire was uniformly employed to ensure the detection of relatively minor events, and all suspected endpoint events (including TIA) were assessed at each study centre by an independent neurologist or stroke physician unaware of randomized treatment assignment and adjudicated by a single, independent, clinical events adjudication committee, also blinded to treatment. Major haemorrhage and MI were similarly adjudicated. Other potential sources of bias included differences in concomitant medication or choice of stroke prevention strategy upon cessation of study medication, but these were relatively minor.

Half the female cohort was ≥75 years of age, a larger proportion than men, and these older women had a higher primary event rate than younger women. Although the results of this subgroup analysis should be interpreted cautiously, they are consistent with reports emerging from other prospectively followed cohorts of patients of both genders with AF. Despite a lower prevalence of diagnosed hypertension, these elderly women had higher systolic blood pressure than men of comparable age, consistent with previous reports.\(^\text{19}\) Although elderly women had more stroke risk factors, there were only small differences in the incidence of prior thrombo-embolism. Despite comparable or greater comorbidities, women were less likely to have taken antithrombotic medication prior to entry, perhaps reflecting fear of anticoagulant-related bleeding among elderly women.\(^\text{20,21}\) In addition, fewer women than men received such concurrent medications as \( \beta \)-blockers, ACE-inhibitors, or lipid-lowering agents at entry or during the course of the studies, yet the all-cause mortality rate during follow-up was higher among men than women. Some of the discrepancy might reflect the less frequent diagnosis of coronary heart disease among women.\(^\text{22}\)

Women had a slightly higher rate of major and minor bleeding than men, but gender did not influence rates of major bleeding and this argues in favour of anticoagulation for women with AF. Compared with younger women, the elderly had similar rates of major bleeding but slightly more overall bleeding than younger women, arguing for anticoagulation of all age groups. The quality of warfarin control was as good among women as in men, with INR values within the INR range of 2–3 about two-thirds of the time on treatment. Warfarin-naive patients may have more events than patients who had taken warfarin previously, as reported in another prospective trial of anticoagulation in patients with AF.\(^\text{23}\) The safety and efficacy we observed during warfarin anticoagulation reflect high-quality management in patients of both genders, and the higher bleeding rates in elderly women cannot be explained by lax INR control.

Few women took ERT during the study periods, possibly because of the reported risks of MI and death in women with CAD taking hormonal therapy,\(^\text{24}\) although more North American women than those in other countries were using ERT. The limited use of ERT among enrolled women makes it difficult to evaluate its impact on the risk of stroke, but we observed no difference in event rates.

The higher primary event rates among women than men were independent of treatment assignment. When examined separately on the basis of ITT, both women and men responded as well to ximelagatran as to well-controlled warfarin for prevention of thrombo-embolism. The efficacy of ximelagatran was also consistent across genders when evaluated by OT analysis. Men had lower rates of major bleeding on ximelagatran than on warfarin, but there were no significant differences in rates of intracerebral haemorrhage, which was infrequent in both genders and in both treatment groups.

Elevations of serum transaminase enzymes occurred more often in women, but rates in both men and women fell within the range reported in other trials involving patients with venous thrombo-embolism and acute coronary syndromes treated with ximelagatran. The mechanism of this reaction is not known, but concerns about potential hepatotoxicity led to withdrawal of ximelagatran from the marketplace.\(^\text{25}\)
The SPORTIF trials represent the largest randomized cohort of women with AF on anticoagulation yet reported, with a high representation of elderly women. As a group, women in the SPORTIF studies were older and had greater comorbidity than in earlier trials of anticoagulation and thus contributed more ischaemic and fatal events for analysis. Although less total bleeding occurred in women on ximelagatran when compared with warfarin, the elevation of liver enzymes offset this benefit. Their clinical features may reflect practice patterns at the time the studies were carried out, yet the differences they exhibited compared with men with AF appear robust across time.

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