Female Sex, Time in Therapeutic Range, and Clinical Outcomes in Atrial Fibrillation Patients Taking Warfarin

Keitaro Senoo, MD; Gregory Y.H. Lip, MD

Background and Purpose—Female patients have higher risk for stroke than male patients in nonanticoagulated atrial fibrillation patients, but limited data are available on sex differences in stroke and bleeding outcomes among patients with anticoagulated atrial fibrillation on warfarin, especially in relation to quality of anticoagulation control, as reflected by the time in therapeutic range (TTR).

Methods—We investigated adverse outcomes in females (n=791) and males (n=1501) among 2292 patients with atrial fibrillation taking warfarin arm in the AMADEUS (Evaluating the Use of SR34006 Compared to Warfarin or Acenocoumarol in Patients With Atrial Fibrillation) trial.

Results—The combined end point of cardiovascular death and stroke/systemic embolism (SSE) was similar in females versus males. There was no sex differences in either cardiovascular death or SSE. Compared with males, females had a lower risk of major bleeding (hazard ratio, 0.39; 95% confidence interval, 0.18–0.87; P=0.02). No differences were seen in mortality and stroke outcomes between females and males either in the prespecified age subgroups or in relation to TTR categories. TTR was negatively correlated with any clinically relevant bleeding in both females (r=−0.86; P=0.03) and males (r=−0.94; P=0.005). On Cox regression, TTR (but not female sex) emerged as an independent predictor for combined cardiovascular death/SSE and clinically relevant bleeding events.

Conclusion—Anticoagulated female patients with atrial fibrillation had a similar rate of cardiovascular death and SSE, but a lower risk of major bleeding, compared with males. TTR (but not female sex) was an independent predictor for combined cardiovascular death and SSE and clinically relevant bleeding events. (Stroke. 2016;47:1665-1668. DOI: 10.1161/STROKEAHA.116.013173.)

Key Words: atrial fibrillation ■ confidence interval ■ sex ■ stroke ■ warfarin

There has been much interest into the importance of sex on prognosis in patients with atrial fibrillation (AF), with females having higher risk of stroke than males.1,2 One meta-analysis suggests that female sex is associated with 1.31-fold increased rate of ischemic stroke/thromboembolism,2 and female patients with AF receiving warfarin may have a higher residual risk of stroke or systemic embolism than male patients.3 This risk could be partly because of poorer oral anticoagulation control among female patients.4 However, the Stroke Prevention Using an Oral Thrombin Inhibitor in Patients With Atrial Fibrillation (SPORTIF) trials found that females with AF had a higher risk of stroke and thromboembolic events despite a similar proportion of time in the therapeutic range (TTR) when compared with males.5 Thus, sex differences in prognosis (ie, stroke, death) in patients with AF taking warfarin are still controversial and little is known about the impact of sex on the relationship between TTR and bleeding outcomes.

Methods

The design of the Evaluating the Use of SR34006 Compared to Warfarin or Acenocoumarol in Patients With Atrial Fibrillation (AMADEUS) trial has previously been described.6 This post hoc analysis used pooled data from the vitamin K antagonist (VKA; ie, warfarin) arm on an intention-to-treat basis. The primary outcome of this analysis was the composite of cardiovascular death and stroke/systemic embolism (SSE). The principal safety outcome of AMADEUS (and used for the present analysis) was centrally adjudicated any clinically relevant bleeding which was defined as major bleeding or nonmajor clinically relevant bleeding. Detailed statistical analyses are described in the online-only Data Supplement.

Results

We studied 2292 patients (791 females) and females were more likely to be older, having more hypertension, less heart failure, and lower mean TTR (Table I in the online-only Data Supplement). After a mean follow-up of 337 days (SD, 165), the primary end point of combined cardiovascular death/SSE occurred in 21 females (2.9%/100 patients-years) and 37 males
Clinical Outcomes in the Study Population

<table>
<thead>
<tr>
<th>Study Outcomes</th>
<th>Female</th>
<th>Male</th>
<th>P Value</th>
<th>P Value (Adjusted*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events/100 Patient-Years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular death or stroke/SE</td>
<td>2.94</td>
<td>2.70</td>
<td>0.73 (0.91 [0.52–1.58])</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>1.18</td>
<td>1.83</td>
<td>0.24 (0.62 [0.28–1.37])</td>
<td></td>
</tr>
<tr>
<td>Stroke/SE</td>
<td>1.96</td>
<td>0.98</td>
<td>0.25 (1.59 [0.73–3.48])</td>
<td></td>
</tr>
<tr>
<td>Any clinically relevant bleeding</td>
<td>11.3</td>
<td>13.2</td>
<td>0.11 (0.79 [0.60–1.05])</td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>1.08</td>
<td>2.28</td>
<td>0.02 (0.39 [0.18–0.87])</td>
<td></td>
</tr>
</tbody>
</table>

Hazard ratio corresponds to the risk of female vs male. CI indicates confidential interval; HR, hazard ratio; and SE, systemic embolism.

*Adjusted HR includes components of CHA2DS2-VASc (congestive heart failure, hypertension, age ≥75 years [double], diabetes mellitus, previous stroke/transient ischemic attack/thromboembolism [double], vascular disease, age 65–74 years, and sex category [score of 1 for females], aspirin use, and time in therapeutic range.

(2.7%/100 patients-years; P=0.73; Table). Cardiovascular death rates were 1.2% and 1.8%/100 patients-years, and SSE rates were 2.0% and 1.0%/100 patients-years, respectively. No differences were seen between females versus males for the end points of cardiovascular death (P=0.24) and SSE (P=0.25).

For bleeding outcomes, any clinically relevant bleeding occurred in 78 females (11.3%/100 patients-years) and 173 males (13.2%/100 patients-years; P=0.11). Major bleeding occurred in 8 females and 31 males (1.1% and 2.3%/100 patients-years, respectively). Females had a lower risk of major bleeding than males (P=0.02).

Sex, Age, and TTR

There were no significant differences in mortality and stroke outcomes between females and males in the prespecified age subgroups. Figure 1 in the online-only Data Supplement shows that females age ≥75 had lower rate of any clinically relevant bleeding (adjusted P=0.04) and females age <75 had a lower rate of major bleeding (P=0.04) compared with males.

TTR was negatively correlated with any clinically relevant bleeding in females (r=-0.86; P=0.03) and males (r=-0.94; P=0.005; Figure). Because of the low number of events, we were limited in power to detect differences between females and males for the TTR<65% and TTR≥65% subgroups; however, numerically lower clinically relevant bleeding events were seen in females compared with males (TTR<65%; females 13.7% versus males 15.7%; TTR≥65%; females 6.6% versus males 9.8%; P value for interaction=0.44).

Multivariate Analysis

For the end point of combined cardiovascular death/SSE events, independent predictors on Cox regression analysis were age (hazard ratio [HR], 1.05; 95% confidence interval [CI], 1.02–1.09; P=0.005), previous stroke/transient ischemic attack (HR, 2.61; 95% CI, 1.55–4.39; P<0.001), and TTR (HR, 0.22; 95% CI, 0.05–0.91; P=0.04). For the end point of clinically relevant bleeding events, independent predictors were use of aspirin (HR, 1.53; 95% CI, 1.14–2.05; P=0.005) and TTR (HR, 0.20; 95% CI, 0.10–0.39; P<0.001).

On logistic regression analysis, determinants of poor TTR (TTR<65%) were previous coronary artery disease in both...
sexes (HR, 1.34, 95% CI, 1.06–1.68, \( P=0.01 \) in males; HR, 1.44, 95% CI, 1.01–2.04, \( P=0.04 \) in females).

**Discussion**

In this study, females had a similar rate of cardiovascular death or SSE, but lower major bleeding than males even after adjustment for differences in baseline characteristics. Second, there were no significant sex differences in outcomes in relation to age category (age<75 and ≥75, respectively) and quality of anticoagulation control (TTR≥65% and ≥65%, respectively). Third, TTR (but not female sex) emerged as an independent predictor for combined cardiovascular death/SSE and clinically relevant bleeding events in the study cohort.

Previous studies of AF have shown varying results, with no differences in cardiovascular morbidity and mortality between females and males,7,8 lower all-cause and cardiovascular mortality in females compared with males,9 or higher mortality in females compared with males.10 In our study, no difference was seen in cardiovascular death/SSE between females and males. The discrepant findings might be because of differences between patient populations studied. Controlled clinical trials usually recruit highly selected patients with various inclusion and exclusion criteria. In our study, all patients required additional risk factors for stroke, thus preselecting a population which could explain some differences, compared with a real-world setting.

Previous studies have shown that females have a higher risk of stroke in patients with AF:6,11,12 In our study, taking into account the higher-risk profile in females, we found no significant differences in stroke and mortality between anticoagulated females and males, even in prespecified age subgroups (age<75 and ≥75, respectively). We therefore suggest that female sex is not an important risk factor for stroke and mortality in chronically anticoagulated patients, at least in this selected trial cohort.

Similar to other trials,9,13 females in this study who were warfarin treated had poorer International Normalized Ratio (INR) control compared with males. Although this could result in females having a higher incidence of stroke/bleeding, this was not seen in this study. On the contrary, a lower incidence of major bleeding was found in females compared with males. We were unable to find a pathophysiological explanation between sex and bleeding outcomes, but one possible reason may be the impact of anticoagulation control on bleeding could be different by sex.4 Although TTR was inversely related to clinically relevant bleeding in our cohort, no statistically significant sex differences were seen.

Unsurprisingly, age, previous stroke, and TTR were independent predictors of cardiovascular death and SSE in our cohort. Of note, aspirin use and poor TTR emerged as independent predictors for any clinically relevant bleeding. These data reinforce the importance of TTR as a predictor of both thromboembolism and bleeding, and emphasizes the importance of good quality anticoagulation control in a patient with AF taking warfarin. An independent determinant of poor TTR was coronary artery disease (irrespective of sex), but this could reflect the tendency of clinicians to use concomitant antiplatelet therapy in such patients and targeting a lower INR range, hence leading to more INR liability (and poorer TTR).

**Limitations**

These results are based on a post hoc analysis of the AMADEUS trial, and should be interpreted as hypothesis generating. The AMADEUS population was at relatively low risk of both ischemic stroke and bleeding events compared with real-world patients, and may have limited statistical power for subgroup comparisons. Initial control of warfarin can be worse in newly diagnosed warfarin-naïve patients (ie, inception phase) and patients in controlled trials may have better TTR compared with real-world clinical practice. The impact of previous warfarin treatment on the outcomes in this study will possibly be less apparent, given our focus on overall TTR, and not just the initial few weeks after the introduction of warfarin. In this study, the lower TTR drives worse outcomes, with a negative linear relationship between TTR and outcomes (Figure). Of note, one-off INR measurements have a poor relationship to the efficacy and safety of warfarin. The TTR reflects the quality of anticoagulation control, with a close inverse relationship of TTR to thromboembolism and bleeding.14,15 Although it is unclear whether the higher bleeding events observed during the low TTR episodes were associated with INRs that were supra/subtherapeutic, evidence suggests that the variability (or instability) of anticoagulation control seems to be the more important determinant. Other factors such as concomitant antiplatelet use, alcohol intake, comorbidities, or other patient behaviors may also be relevant.

In conclusion, anticoagulated female patients with AF had a similar rate of cardiovascular death, stroke, or systemic embolism on warfarin, but a lower risk of major bleeding compared with males. TTR (but not female sex) was an independent predictor for combined cardiovascular death/SSE and clinically relevant bleeding events.

**Disclosures**

Dr Lip is a Consultant at Bayer/Janssen, Astellas, Merck, Sanofi, BMS/Pfizer, Biotronik, Medtronic, Portola, Boehringer Ingelheim, Microlife, and Daiichi-Sankyo; speaker in Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche, and Daiichi-Sankyo. The other author reports no conflicts.

**References**


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The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/47/6/1665

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2016/05/18/STROKEAHA.116.013173.DC1

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Statistical analysis

Characteristics of the patients are reported as percentages and mean ± standard deviation (SD). Comparisons between females and males were made using Fisher’s exact test when comparing categorical variables and Mann-Whitney’s U test for continuous variables. Outcomes by age-group were calculated by the overall rate of adverse events per 100 patient-years. We used Cox proportional hazard models to estimate the hazard ratios for adverse outcomes. Correlations and regression analysis was performed between TTR and clinically relevant bleeding by gender, and logistic regression analysis performed to assess determinants of poor TTR (ie. TTR<65%). A two-tailed p-value <0.05 was considered statistically significant. Analyses were performed using SPSS(version 21).
### Supplementary Table I

Clinical characteristics of the Study Population

<table>
<thead>
<tr>
<th></th>
<th>Female</th>
<th>Male</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>791</td>
<td>1501</td>
<td></td>
</tr>
<tr>
<td>Age, years(± SD)</td>
<td>72.1(8.4)</td>
<td>69.2(9.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension(%)</td>
<td>667(84.3)</td>
<td>1097(73.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart failure(%)</td>
<td>114(14.4)</td>
<td>429(28.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus(%)</td>
<td>165(20.9)</td>
<td>285(19)</td>
<td>0.45</td>
</tr>
<tr>
<td>Previous stroke, TIA or TE(%)</td>
<td>215(27.2)</td>
<td>360(24)</td>
<td>0.19</td>
</tr>
<tr>
<td>Coronary artery disease(%)</td>
<td>221(27.9)</td>
<td>497(33.1)</td>
<td>0.03</td>
</tr>
<tr>
<td>Creatinine clearance(±SD)</td>
<td>66.3(27.4)</td>
<td>81.7(32.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aspirin(%)</td>
<td>111(14)</td>
<td>268(17.9)</td>
<td>0.05</td>
</tr>
<tr>
<td>Time in Therapeutic Range(±SD)</td>
<td>55.7(19.7)</td>
<td>58.1(20.2)</td>
<td>0.005</td>
</tr>
<tr>
<td>CHADS&lt;sub&gt;2&lt;/sub&gt; score</td>
<td>2.2(1.1)</td>
<td>2.0(1.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CHA&lt;sub&gt;2&lt;/sub&gt;DS&lt;sub&gt;2&lt;/sub&gt;-VASc score</td>
<td>4.3(1.4)</td>
<td>3.0(1.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HAS-BLED score</td>
<td>1.98(0.96)</td>
<td>1.76(1.0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

TIA; transient ischemic attack, TE; thromboembolism, SD; standard deviation  
CHADS<sub>2</sub> score; congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, and previous stroke/transient ischemic attack,  
CHA<sub>2</sub>DS<sub>2</sub>-VASc score; congestive heart failure, hypertension, age ≥75 years [double score], diabetes mellitus, previous stroke/TIA (double score), vascular disease, age 65-74 years, sex category (female),  
HAS-BLED score; Hypertension, Abnormal renal/liver function, Stroke, Bleeding history, Labile international normalized ratio (INR), Elderly (age >65 years), drugs or alcohol concomitant
Supplementary Figure I

Mortality, stroke and bleeding outcomes in females and males according to age category