Does Sex Affect Anticoagulant Use for Stroke Prevention in Nonvalvular Atrial Fibrillation?

The Prospective Global Anticoagulant Registry in the FIELD-Atrial Fibrillation

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Background—Among patients with atrial fibrillation (AF), women are at higher risk of stroke than men. Using prospective cohort data from a large global population of patients with nonvalvular AF, we sought to identify any differences in the use of anticoagulants for stroke prevention in women and men.

Methods and Results—This was a prospective multicenter observational registry with 858 randomly selected sites in 30 countries. A total of 17,184 patients with newly diagnosed (≤6 weeks) nonvalvular AF and ≥1 additional investigator-defined stroke risk factor(s) were recruited (March 2010 to June 2013). The main outcome measure was the use of anticoagulants (vitamin K antagonists, factor Xa inhibitors, and direct thrombin inhibitors) for stroke prevention at AF diagnosis. Of 17,184 patients enrolled, 43.8% were women. More women than men were at moderate-to-high risk of stroke (CHADS² score ≥2: 65.1% versus 54.7%). Rates of anticoagulant use were not different overall (60.9% of men versus 60.8% of women) and in patients with a CHADS² score ≥2 (adjusted odds ratio for women versus men, 1.00; 95% confidence interval, 0.92–1.09). In patients at low risk (CHADS²-VASc of 0 in men and 1 in women), 41.8% of men and 41.1% of women received an anticoagulant. In patients at high risk (CHADS²-VASc score ≥2), 35.4% of men and 38.4% of women did not receive an anticoagulant.

Conclusions—These contemporary global data show that anticoagulant use for stroke prevention is no different in men and women with nonvalvular AF. Thromboprophylaxis was, however, suboptimal in substantial proportions of men and women, with underuse in those at moderate-to-high risk of stroke and overuse in those at low risk.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01090362.

Key Words: atrial fibrillation ■ embolism ■ sex ■ stroke ■ women

Among patients with atrial fibrillation (AF), women tend to be at higher risk of stroke than men, even after adjustment for baseline comorbidity conditions and vitamin K antagonist treatment. Female sex has therefore been incorporated in stroke risk stratification schemes, such as CHADS²-VASc (Cardiac failure or dysfunction, Hypertension, Age ≥75 [Double], Diabetes, Stroke [Double]-Vascular disease, Age 65–74, and Sex category [Female]), and is specified in international guidelines for stroke prevention in AF.

Women have a longer life expectancy than men and therefore comprise a larger proportion of the elderly population who are at risk of stroke caused by AF. As such, women represent an important target for preventive strategies. Women are under-represented in mixed-sex cardiovascular trials, resulting in a deficit of information on differences in treatment effect and in side-effect profiles.

Using data from a large contemporary prospective cohort study of patients newly diagnosed with non-valvular AF, we investigated the use of anticoagulants for stroke prevention in women and men, according to validated stroke and bleeding risk stratification schemes: CHADS² (Congestive heart failure, Hypertension, Age >75 years, Diabetes mellitus, and prior...
**WHAT IS KNOWN**

- Women with atrial fibrillation are at higher risk of stroke than men with atrial fibrillation.
- The reasons for this elevated risk remain unclear, but they may include older age of women, use of hormone replacement therapy, undertreatment or suboptimal management with a vitamin K antagonist, and poor anticoagulation control.

**WHAT THE STUDY ADDS**

- The results from our worldwide study suggest that women are treated no differently to men in terms of anticoagulant therapy for stroke prevention.
- Thromboprophylaxis was, however, suboptimal in substantial proportions of men and women, with underuse in those at moderate-to-high risk of stroke and overuse in those at low risk.
- Improvements in anticoagulation prescription and management are needed for women and men.

Stroke or transient ischemic attack [Double], CHA\_DS\_2-VASc\_9 and HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio [INR], Elderly, Drugs/alcohol concomitantly). We hypothesized that anticoagulant use in women would be lower than that in men using data from the Global Anticoagulant Registry in the FIELD-Atrial Fibrillation (GARFIELD-AF).

**Methods**

**Design**

GARFIELD-AF is an ongoing, observational, worldwide study of adults with recently diagnosed nonvalvular AF. Independent ethics committee and hospital-based institutional review board approvals were obtained, as necessary, for the registry protocol. The registry is being conducted in accordance with the principles of the Declaration of Helsinki, local regulatory requirements, and the International Conference on Harmonisation-Good Pharmacoepidemiological and Clinical Practice Guidelines. All patients provided written informed consent to participate. Confidentiality and anonymity of all patients enrolled into this registry are maintained at all times.

**Study Population**

Men and women aged ≥18 years with nonvalvular AF diagnosed according to standard local procedures within the past 6 weeks and with ≥1 additional factor(s) for stroke as judged by the investigator were eligible for enrollment. These risk factors were not prespecified in the protocol nor were they limited to the components of existing risk stratification schemes. Patients with a transient reversible cause of AF and those for whom follow-up to 2 years was unlikely were excluded. Data were collected using an electronic case report form. Patient enrollment was consecutive. Patients are being enrolled prospectively into 5 subsequent cohorts, each comprising ≈10000 patients. Cohort 1 included a validation cohort of 5000 patients, enrolled at the same time as the first cohort, to describe the nature and characteristics of care for patients at participating sites before registry initiation; these patients were enrolled retrospectively and were excluded from the present analysis. This article reports only cross-sectional data at baseline.

**Study Sites**

A 3-step process was used for site selection to ensure proportional representation of the spectrum of care settings in each country. First, the national coordinating investigator identified the care settings, including office-based practice, hospital departments (neurology, cardiology, geriatrics, internal medicine, and emergency), anticoagulation clinics, and general or family practices, they believed most accurately represented the management of AF patients in their country. Second, the contract research organization provided a list (sampling frame) of sites from various database searches that reflected the care settings in the country. Third, the contract research organization contacted a random (i.e., lack of selection of sites based on specific criteria rather than using random sampling) sample of sites for each care setting from the list, in accordance with the distribution specified by the national coordinating investigator. Sites that agreed to participate were recruited after a qualification telephone call, and the relevant investigator was required to complete a program providing guidance on patient screening, enrollment, and follow-up in the registry.

**Data**

Registry data were captured by trained data abstractors in electronic case report forms (designed by Dendrite Clinical Systems Ltd, Henley-on-Thames, United Kingdom, which is also responsible for ongoing database program management). Data collection and entry are managed by Quintiles (Durham, NC), which oversees all operational aspects of the program, apart from in the United Kingdom, where the tasks are undertaken by The University of Birmingham Department of Primary Care Clinical Sciences. Submitted data are examined by the coordinating center (Thrombosis Research Institute, London, United Kingdom) to ascertain their completeness and accuracy, and data queries are sent to participating sites. Data for this analysis, extracted on February 3, 2014, were analyzed by a statistician (Gabriele Accetta). The GARFIELD-AF registry uses a combination of techniques for quality control in monitoring of this study: frequent electronic database monitoring of all data entered into the registry database; remote site monitoring by clinical research associates on a monthly, quarterly, or 6-monthly basis depending on the site; on-site monitoring, which includes source document verification as per the monitoring plan; and ongoing monitoring of quality by the Audit Committee (Data Supplement).

**Definitions**

The term anticoagulation encompasses vitamin K antagonists, oral, injectable or undefined factor Xa inhibitors, and direct thrombin inhibitors. Vascular disease was defined as peripheral artery disease or coronary artery disease with a history of acute coronary syndrome (unstable angina or myocardial infarction). Hypertension was defined as a documented history of hypertension or blood pressure >140/90 mmHg.

**Statistical Analysis**

Continuous variables are expressed as mean±SD or median (interquartile range) and categorical variables as frequency and percentage. Reported use at baseline of antithrombotic therapies was analyzed in relation to sex, according to CHADS\_2,\_15 CHA\_DS\_2-VASc\_9 and modified HAS-BLED (excluding fluctuations in the international normalized ratio) scores, calculated retrospectively from the data provided. For patients with a CHADS\_2 score of ≥2, the strength of the association between independent factors and use of anticoagulation is expressed using odds ratios (ORs). Uncertainty related to OR estimates was assessed using 95% confidence intervals. Logistic regression models with only one independent factor as the explanatory variable in each were fitted to estimate crude ORs (univariate models). Adjusted ORs were estimated using a multivariable model. The models included variables judged to be of clinical relevance: sex, age, previous stroke, history of hypertension, congestive heart failure, diabetes mellitus, vascular disease, and geographic region. HAS-BLED
was not included in the models because of a high number of missing values. Patients with any missing values for confounders or unknown anticoagulant use did not contribute to the models. Age was categorized into 5 groups: ≤55, >55 to ≤65, >65 to ≤75, >75 to ≤85, and >85 years. Three different regions were included in the models: Europe (Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Hungary, Italy, the Netherlands, Norway, Poland, Russia, Spain, Sweden, Ukraine, and United Kingdom), Asia (China, India, Japan, Korea, Singapore, and Thailand), and non-Europe/non-Asia (Argentina, Australia, Brazil, Canada, Chile, Mexico, and South Africa). All other variables were treated as dichotomous, having only 2 possible values of yes and no. Adjusted ORs for risk factors were compared between women and men, fitting a model with first-degree interaction between sex and all other factors. Data analysis was performed with SAS statistical software, release 9.4 (SAS Institute Inc, Cary, NC).

Results

Study Population

Enrollment took place at 858 randomly selected sites in 30 countries in Europe (n=10851; 63.1%), Asia (n=3949; 23.0%), Central/South America (n=1443; 8.4%), Canada (n=348; 2.0%), Australia (n=427; 2.5%), and South Africa (n=166; 1.0%) between March 2, 2010, and June 7, 2013 (Table 1). Baseline characteristics for the 17184 patients are shown in Table 2. Of this population, 7530 (43.8%) were women. Women were older than men, with 47.5% aged ≥75 years versus 30.6% of men, and were less likely to be current or past smokers or heavy alcohol drinkers and to have coronary artery disease, peripheral artery disease, or a left ventricular ejection fraction of <40%. Women had higher prevalences of history of hypertension and moderate renal disease (ie, estimated glomerular filtration rate of 30–59 mL/min) and higher mean CHA2DS2-VASc scores because of their sex. A greater proportion of the women were at moderate-to-high risk of stroke (CHADS2 score of ≥2; 65.1% versus 54.7% of men). Almost all of the women (97.3%) had a CHA2DS2-VASc score of ≥2 versus 77.1% of the men. Of the 10882 patients in whom the HAS-BLED score could be calculated, 12.3% of men and 14.1% of women had a score of ≥3; the mean scores were similar in men and women.

Antithrombotic Therapy Use in Men and Women Overall and According to Risk Scores

Antithrombotic drugs given at diagnosis of AF are detailed in Table 3 and Figure 1. Aspirin was given to >30% of both men and women and adenosine diphosphate receptor inhibitors/P2Y12 inhibitors to 8.0% of men and 6.2% of women. Overall rates of anticoagulant use were no different in men and women (5788/9509 [60.9%] versus 4498/7404 [60.8%], respectively; Figure 1); 11.8% of men and 11.7% of women were receiving a factor Xa inhibitor or direct thrombin inhibitor (Table 3). Twenty-eight percent of men and 27.2% of women received an antiplatelet alone, and 12% of both men and women received no antithrombotic therapy. When analyzed by the level of stroke risk, approximately half of the men and women at low risk of stroke received some form of anticoagulant therapy, with similar patterns of antithrombotic use in men and women (Figure 2A). Among those with a CHADS2 score of 1, men had slightly higher levels of anticoagulant use compared with women. In patients with a CHADS2 score of ≥2, men were more likely than women to receive the combination of anticoagulant plus antiplatelet, but the overall rates of anticoagulant use were similar. After adjustment, use of an anticoagulant for stroke prevention in patients with a CHADS2 score of ≥2 was the same in women and men (OR, 1.00; 95% confidence interval, 0.92–1.09).

In patients with a low risk of stroke, 41.8% (158/378) of men (CHA2DS2-VASc score of 0) and 41.1% (81/197) of women (CHA2DS2-VASc score of 1) received an anticoagulant (Figure 2B); the rate of antiplatelet use alone was slightly higher in women. In patients at high risk of stroke (CHA2DS2-VASc score of ≥2), 64.6% (4593/7108) of men and 61.6% (4329/7032) of women received an anticoagulant.
Table 2. Baseline Characteristics in Men and Women With Nonvalvular Atrial Fibrillation (n=17184)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men (n=9654)</th>
<th>Women (n=7530)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Mean (SD), y</td>
<td>68/9654 (12)</td>
<td>73/7530 (10)</td>
</tr>
<tr>
<td>Age group, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 y</td>
<td>3560/9654 (36.9)</td>
<td>1550/7530 (20.6)</td>
</tr>
<tr>
<td>65–74 y</td>
<td>3144/9654 (32.6)</td>
<td>2400/7530 (31.9)</td>
</tr>
<tr>
<td>≥75 y</td>
<td>2950/9654 (30.6)</td>
<td>3580/7530 (47.5)</td>
</tr>
<tr>
<td>Body mass index Mean (SD), kg/m²</td>
<td>27.7 (4.9)</td>
<td>27.8 (5.9)</td>
</tr>
<tr>
<td>Body mass index Missing data, n (%)</td>
<td>914 (9.5)</td>
<td>670 (8.9)</td>
</tr>
<tr>
<td>Pulse Median (IQR), bpm</td>
<td>82.0 (70.0–100.0)</td>
<td>85.0 (70.0–110.0)</td>
</tr>
<tr>
<td>Pulse Missing data, n (%)</td>
<td>667 (6.9)</td>
<td>544 (7.2)</td>
</tr>
<tr>
<td>Systolic blood pressure Mean (SD), mm Hg</td>
<td>130.0 (120.0–144.0)</td>
<td>134.0 (120.0–148.0)</td>
</tr>
<tr>
<td>Systolic blood pressure Missing data, n (%)</td>
<td>667 (6.9)</td>
<td>544 (7.2)</td>
</tr>
<tr>
<td>Diastolic blood pressure Median (IQR), mm Hg</td>
<td>80.0 (70.0–89.0)</td>
<td>80.0 (70.0–88.0)</td>
</tr>
<tr>
<td>Diastolic blood pressure Missing data, n (%)</td>
<td>349/8258 (4.2)</td>
<td>28/6494 (0.4)</td>
</tr>
<tr>
<td>Heavy alcohol consumption, n (%)</td>
<td>1769/9373 (18.9)</td>
<td>200/7352 (2.7)</td>
</tr>
<tr>
<td>Medical history, n (%)</td>
<td>63/9648 (0.7)</td>
<td>30/7527 (0.4)</td>
</tr>
<tr>
<td>Acute coronary syndromes</td>
<td>1103/9652 (11.4)</td>
<td>520/7527 (6.9)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>292/9649 (3.0)</td>
<td>203/7526 (2.7)</td>
</tr>
<tr>
<td>Carotid occlusive disease</td>
<td>294/9649 (3.0)</td>
<td>207/7526 (2.8)</td>
</tr>
<tr>
<td>Chronic renal disease</td>
<td>2544/7110 (26.4)</td>
<td>1845/5685 (24.5)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction &lt;40%</td>
<td>734/5638 (13.0)</td>
<td>247/4125 (6.0)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2127/9653 (22.0)</td>
<td>1634/7529 (21.7)</td>
</tr>
<tr>
<td>Family history of premature cardiac disease†</td>
<td>1666/8008 (20.8)</td>
<td>1379/6219 (22.2)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>3790/9648 (39.3)</td>
<td>3090/7528 (41.0)</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>7303/9653 (75.7)</td>
<td>6114/7529 (81.2)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction &lt;40%</td>
<td>734/5638 (13.0)</td>
<td>247/4125 (6.0)</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>719/9648 (7.5)</td>
<td>406/7526 (5.4)</td>
</tr>
<tr>
<td>Pulmonary embolism or DVT</td>
<td>221/9651 (2.3)</td>
<td>255/7526 (3.4)</td>
</tr>
<tr>
<td>Stroke or TIA</td>
<td>1185/9653 (12.3)</td>
<td>993/7529 (13.2)</td>
</tr>
<tr>
<td>Stroke</td>
<td>811/9652 (8.4)</td>
<td>640/7526 (8.5)</td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>59/9652 (0.6)</td>
<td>52/7525 (0.7)</td>
</tr>
<tr>
<td>Other thromboembolism‡</td>
<td>99/9593 (1.0)</td>
<td>81/7470 (1.1)</td>
</tr>
<tr>
<td>Hormone replacement therapy</td>
<td>35/9654 (0.4)</td>
<td>119/7530 (1.6)</td>
</tr>
<tr>
<td>Risk score CHADS&lt;sub&gt;2&lt;/sub&gt; Missing data, n (%)</td>
<td>229 (2.4)</td>
<td>128 (1.7)</td>
</tr>
<tr>
<td>Risk score Mean (SD)</td>
<td>1.8 (1.1)</td>
<td>2.0 (1.1)</td>
</tr>
<tr>
<td>Risk score Median (IQR)</td>
<td>2.0 (1.0–2.0)</td>
<td>2.0 (1.0–3.0)</td>
</tr>
<tr>
<td>Risk score 0, n (%)</td>
<td>735/9425 (7.8)</td>
<td>383/7352 (5.2)</td>
</tr>
<tr>
<td>Risk score 1, n (%)</td>
<td>3538/9425 (37.5)</td>
<td>2197/7352 (29.7)</td>
</tr>
<tr>
<td>Risk score ≥2, n (%)</td>
<td>5152/9425 (54.7)</td>
<td>4822/7352 (65.1)</td>
</tr>
</tbody>
</table>

*Investigator-defined.
†First-degree relative with premature cardiac history (age <55 y [men]; <65 y [women]).
‡For example, central venous thrombosis and retinal occlusion.
§Excluding international normalized ratio fluctuations.

CHA<sub>DS</sub>-VASc indicates cardiac failure or dysfunction, hypertension, age ≥75 [double], diabetes mellitus, stroke [double]-vascular disease, age 65–74, and sex category [female]; CHADS<sub>3</sub> indicates congestive heart failure, hypertension, age >75 years, diabetes mellitus, and previous stroke or transient ischemic attack [double]; DVT, deep vein thrombosis; GFR, glomerular filtration rate; HAS-BLED hypertension, abnormal renal/liver function, stroke, bleeding history, or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly; IQR, interquartile range; and TIA, transient ischemic attack.

The use of antithrombotic drugs according to bleeding risk stratum is shown in Figure 3. Of the 17184 patients, 6302 (36.7%) had values missing for components of the HAS-BLED score. Similar patterns of use were observed when comparing men with women, in both the low-risk (HAS-BLED score of 0–2) and high-risk (HAS-BLED score of ≥3) groups. The overall rate of use of anticoagulants was higher in patients at low risk of bleeding (3346/5203 [64.3%] men and 2694/4087 [65.9%] women) when compared with those at high risk (377/729 [51.7%] and 349/673 [51.9%], respectively). Both men and women at high risk of bleeding were more likely than those at low risk to receive combination antithrombotic therapy or antiplatelet therapy alone.
The main reasons for not giving an anticoagulant to patients at moderate-to-high risk of stroke (CHADS2 score of ≥2) were similar between men and women and were largely because of physician choice (Table 4).

Anticoagulant Use in Subgroups at Risk of Stroke

The univariate ORs for anticoagulant use in various subgroups of patients with a CHADS2 score of ≥2 are provided in Table 5, and the adjusted data for men and for women are presented in Figure 4. After adjustment, patients aged ≥85 years appeared to have a lower rate of use of anticoagulants than those aged ≤55 years, but the difference was not significant. Anticoagulant use was decreased in men and women aged ≥85 years. Men and women with a previous stroke were more likely than those without to receive anticoagulant treatment, whereas men and women with a history of hypertension were less likely to receive anticoagulants than those without a history.

Discussion

In this large, contemporary, prospective, global cohort study of patients with newly diagnosed nonvalvular AF, overall use of anticoagulant therapy for stroke prevention was no different in men and women. Among patients with a CHADS2 score of 1, women were less likely than men to receive combination antithrombotic therapy. Use of anticoagulants in patients with a CHADS2 score of 0 could reflect suboptimal adherence by patient or provider.
of more intensive therapy in such patients may be somewhat unexpected, given that it is associated with an increased risk of bleeding complications, it probably reflects overlapping risk factors in stroke and bleeding risk scores. The presence of concomitant conditions such as coronary artery disease cannot, alone, account for the high rates of use of combination therapy in men and women at high risk of bleeding. Furthermore, a high HAS-BLED score per se should not be used to withdraw or preclude the use of anticoagulants; rather, it should be used to identify patients at higher risk of bleeding and to correct any potentially reversible risk factors for this event, and, in particular, to reconsider the use of combination antithrombotic therapy.

Reasons for the increased risk of stroke in women are uncertain. Stroke risk may be age dependent because, compared with that in men, it is increased only in women ≥65 years of age. Hormone replacement therapy may be a risk factor for ischemic stroke. Undertreatment or suboptimal management with an oral anticoagulant is also a possibility, with poor average time in the therapeutic range and frequent interruptions in anticoagulant therapy possibly contributing to the higher risk of stroke in women. The ORs for anticoagulant use in subgroups of men and women were similar, with the exception of men with a previous stroke or aged 65 to 75 years who were more likely to receive anticoagulants, whereas women with congestive heart failure and men with a history of hypertension were less likely to receive anticoagulants.

The GARFIELD-AF data show some similarities with the Euro Heart Survey on AF, which was conducted between 2003 and 2004, and involved 5333 patients with AF from 35 European Society of Cardiology countries. Although the use of anticoagulants in men and women was similar, several differences were apparent: women were older than men and had a higher prevalence of comorbid conditions. Men and women in the GARFIELD-AF registry were, however, older (68 and 73 years, respectively) than those in the Euro Heart Survey on AF (64 and 70 years, respectively), and they had a lower prevalence of congestive heart failure and coronary artery disease but a higher prevalence of hypertension and previous stroke, suggesting temporal, ascertainment, and geographic differences between these study populations.

The prospective GARFIELD-AF registry is the largest worldwide initiative to study the risk of stroke among patients with newly diagnosed nonvalvular AF. The present analysis includes data spanning 30 countries across 6 continents. The population is representative of the spectrum of patients treated in everyday practice in each of the countries. This analysis is, however, limited by its observational design, although great efforts were made to standardize definitions of conditions, and missing data. No information has been included on race. The percentage of low-risk patients who were overtreated may have been overestimated, as the primary indication for anticoagulant use was not recorded, no data were available for patients with a mechanical heart valve, and history of cardioversion or ablation was known for few patients (146 and 152, respectively). Of the low-risk patients (CHADS2 score of 0), only 10 men and 5 women had a history of venous thromboembolism. Recruitment preceded publication of the European Society of Cardiology 2010 guidelines on stroke prevention, which suggests the use of

### Table 4. Main Reasons Why Vitamin K Antagonists Were Not Given to Men and Women With a CHADS2 Score of ≥2 (n=2643)

<table>
<thead>
<tr>
<th>Reason, n (%)</th>
<th>Men (n=1349)</th>
<th>Women (n=1294)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician’s choice</td>
<td>625 (46.3)</td>
<td>639 (49.4)</td>
</tr>
<tr>
<td>Bleeding risk</td>
<td>111 (17.8)</td>
<td>94 (14.7)</td>
</tr>
<tr>
<td>Concern over patient compliance</td>
<td>71 (11.4)</td>
<td>67 (10.5)</td>
</tr>
<tr>
<td>Guideline recommendation</td>
<td>15 (2.4)</td>
<td>20 (3.1)</td>
</tr>
<tr>
<td>Fall risk</td>
<td>49 (7.8)</td>
<td>123 (19.2)</td>
</tr>
<tr>
<td>Low risk of stroke</td>
<td>67 (10.7)</td>
<td>52 (8.1)</td>
</tr>
<tr>
<td>Not specified</td>
<td>312 (49.9)</td>
<td>283 (44.3)</td>
</tr>
<tr>
<td>Patient refusal</td>
<td>119 (8.8)</td>
<td>112 (8.7)</td>
</tr>
<tr>
<td>Already taking antiplatelet drugs for other medical conditions</td>
<td>91 (6.7)</td>
<td>68 (5.3)</td>
</tr>
<tr>
<td>Previous bleeding event</td>
<td>26 (1.9)</td>
<td>25 (1.9)</td>
</tr>
<tr>
<td>Alcohol misuse</td>
<td>13 (1.0)</td>
<td>2 (0.2)</td>
</tr>
<tr>
<td>Taking medication contraindicated or cautioned for use with vitamin K antagonist or anticoagulants</td>
<td>7 (0.5)</td>
<td>6 (0.5)</td>
</tr>
<tr>
<td>Other or unknown</td>
<td>468 (34.7)</td>
<td>442 (34.2)</td>
</tr>
</tbody>
</table>

To guidelines, or it may simply indicate that many clinicians think a CHADS2 score of 0 is not low risk and informally consider other risk factors when assessing risk. Among truly low-risk patients (CHA2DS2-VASc score of 0 in men and 1 in women), who are not considered candidates for anticoagulant therapy according to the guidelines, ~40% received an anticoagulant. In contrast, among those with a CHA2DS2-VASc score of ≥2, in whom anticoagulation is a class I recommendation, one-third did not receive an anticoagulant. Of the women with a CHA2DS2-VASc score of 0, 41.1% were prescribed anticoagulants (some in combination with an antiplatelet) and 34.5% received an antiplatelet alone. Only 24.4% received no antithrombotic therapy, consistent with guideline recommendations. The rate of use of antiplatelet therapy does not correlate with the rates of cardiovascular diseases among women, indicating that antiplatelets are still being given to low-risk women for stroke prevention, thus increasing bleeding risk. Similarly, 41.8% of men with a CHA2DS2-VASc score of 0 were prescribed anticoagulant therapy, and only 28.3% received no antithrombotic therapy. These findings of suboptimal thromboprophylaxis are of concern and indicate the need for improved stroke prevention in AF. These observations were evident from registries conducted a decade ago and show that anticoagulant use remains suboptimal in both sexes, reflecting the many limitations and difficulties with using vitamin K antagonists, and despite the recent introduction of direct anticoagulants.

Estimating bleeding risk in patients with AF can be difficult. The use of risk scores, such as HAS-BLED, may help clinicians make an informed decision about a patient’s potential risk for bleeding. In this study, the patterns of use of antithrombotic therapy were broadly similar when comparing men with women at low or high risk of a bleed. The overall rates of anticoagulant therapy were higher in the low-risk group. However, combination antithrombotic therapy was more frequent in the high-risk group. Although the use...
the CHA2DS2-VASc score to determine stroke risk. The results for the HAS-BLED score should be interpreted with caution because of the high number of missing values.

Conclusions
Overall rates of anticoagulant use in nonvalvular AF are no different in men and women. The results indicate suboptimal application of thromboprophylaxis in large proportions of men and women with AF, with underuse in moderate-to-high-risk patients and overuse in low-risk patients. Improvements in stroke prevention, as well as stroke and bleeding risk assessment, are clearly needed in men and women with AF.

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Disclosures
Dr Lip is a consultant for Bayer, Astellas, Merck, Sanofi, Bristol-Myers Squibb/Pfizer, Daiichi-Sankyo, Biotronik, Medtronic, Portola, and Boehringer Ingelheim, and he is a Speakers’ Bureau member for Bayer, BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, and Medtronic. Dr Rushton-Smith is a consultant for Bristol-Myers Squibb, Boehringer-Ingelheim, MSD, Sanofi, and Servier. Dr Goldhaber received research support from Bristol-Myers Squibb, Daiichi Sankyo, BTG, and National Heart, Lung, and Blood Institute, and he is a consultant/advisory board member for Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Janssen, and Portola. Dr Fitzmaurice received honoraria from Bayer, Boehringer Ingelheim, and sanofi-aventis. Dr Mantovani is a consultant for Bayer HealthCare Pharmaceuticals and received grants from Boehringer Ingelheim, Pfizer, BMS, and Daiichi Sankyo. Dr Goto received research grants from sanofi-aventis (significant) and Pfizer (modest); he is a consultant for Bristol-Myers Squibb (modest), a Speakers’ Bureau member for Bristol-Myers Squibb/Pfizer (modest) and also received honoraria from Bayer, Daiichi Sankyo, and Bristol-Myers Squibb/Pfizer (modest), and sanofi-aventis (significant). Dr Haas received honoraria

Table 5. Use of Anticoagulants in Subgroups With Atrial Fibrillation and CHADS2 Score ≥2: Univariate Analysis (n=9974), where an Odds Ratio of >1 Indicates Higher Probability to Use

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Category</th>
<th>%</th>
<th>n</th>
<th>N*</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td>Men (ref.)</td>
<td>66.0</td>
<td>3386</td>
<td>5133</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>65.7</td>
<td>3147</td>
<td>4791</td>
<td>0.99 (0.91–1.07)</td>
</tr>
<tr>
<td><strong>Age group, y</strong></td>
<td>≤55 (ref.)</td>
<td>61.9</td>
<td>340</td>
<td>549</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>55–65</td>
<td>64.9</td>
<td>922</td>
<td>1420</td>
<td>1.14 (0.93–1.40)</td>
</tr>
<tr>
<td></td>
<td>65–75</td>
<td>67.6</td>
<td>1833</td>
<td>2713</td>
<td>1.28 (1.06–1.55)</td>
</tr>
<tr>
<td></td>
<td>75–85</td>
<td>67.2</td>
<td>2920</td>
<td>4343</td>
<td>1.26 (1.05–1.52)</td>
</tr>
<tr>
<td></td>
<td>&gt;85</td>
<td>57.6</td>
<td>518</td>
<td>899</td>
<td>0.84 (0.67–1.04)</td>
</tr>
<tr>
<td><strong>Geographic region</strong></td>
<td>Asia† (ref.)</td>
<td>55.2</td>
<td>1051</td>
<td>1904</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Europe‡</td>
<td>69.7</td>
<td>4589</td>
<td>6585</td>
<td>1.87 (1.68–2.07)</td>
</tr>
<tr>
<td></td>
<td>Non-Europe/non-Asia§</td>
<td>62.2</td>
<td>893</td>
<td>1435</td>
<td>1.34 (1.16–1.54)</td>
</tr>
<tr>
<td>**Previous stroke</td>
<td></td>
<td>**</td>
<td>No (ref.)</td>
<td>65.3</td>
<td>5552</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>68.8</td>
<td>979</td>
<td>1424</td>
<td>1.17 (1.03–1.32)</td>
</tr>
<tr>
<td><strong>History of hypertension</strong></td>
<td>No (ref.)</td>
<td>69.3</td>
<td>735</td>
<td>1060</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>65.4</td>
<td>5798</td>
<td>8864</td>
<td>0.84 (0.73–0.96)</td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td>No (ref.)</td>
<td>65.8</td>
<td>4224</td>
<td>6421</td>
<td>1</td>
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<tr>
<td></td>
<td>Yes</td>
<td>65.9</td>
<td>2309</td>
<td>3503</td>
<td>1.01 (0.92–1.10)</td>
</tr>
<tr>
<td><strong>Vascular disease##</strong></td>
<td>No (ref.)</td>
<td>65.9</td>
<td>5979</td>
<td>9076</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>65.3</td>
<td>554</td>
<td>848</td>
<td>0.98 (0.84–1.13)</td>
</tr>
<tr>
<td><strong>Congestive heart failure</strong></td>
<td>No (ref.)</td>
<td>66.6</td>
<td>4408</td>
<td>6621</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>64.3</td>
<td>2125</td>
<td>3303</td>
<td>0.91 (0.83–0.99)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; and ref., reference category.
*Fifty patients with missing data on anticoagulant use were removed.
†China, India, Japan, Korea, Singapore, and Thailand.
‡Austria, Czech Republic, Belgium, Denmark, Finland, France, Germany, Hungary, Italy, the Netherlands, Norway, Poland, Russia, Spain, Sweden, Ukraine, and United Kingdom.
§Argentina, Brazil, Chile, Mexico, Australia, Canada, and South Africa.
||Three patients with missing data on stroke were removed.
#Three patients with missing data on vascular disease were removed.
Figure 4. Use of anticoagulants at baseline in subgroups of men and women with a CHADS2 score of ≥2 (n=9974). *Reference group, no history. Fifty patients with missing data on anticoagulant use were removed. Four patients with missing data for independent variables were also removed. Likelihood ratio tests were performed to test the gain in the likelihood because of each interaction term. Interaction terms with sex were not statistically significant (P>0.05). Only the interaction term between sex and diabetes mellitus showed a P value of <0.1 (P=0.06). CI indicates confidence interval; OR, odds ratio; and ref., reference group.

Appendix

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References


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