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 ($CHADS_2$ 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 $CHADS_2$ score ≥2 (adjusted odds ratio for women versus men, 1.00; 95% confidence interval, 0.92–1.09). In patients at low risk (CHA_2DS_2-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 (CHA_2DS_2-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.

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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,[1–6] even after adjustment for baseline comorbid conditions and vitamin K antagonist treatment.[7,8] Female sex has therefore been incorporated in stroke risk stratification schemes, such as CHA_2DS_2-VASc (Cardiac failure or dysfunction, Hypertension, Age ≥75 [Double], Diabetes, Stroke [Double]-Vascular disease, Age 65–74, and Sex category [Female]),[9] and is specified in international guidelines for stroke prevention in AF.[10–12]

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.[13] 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.[14]

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: $CHADS_2$ (Congestive heart failure, Hypertension, Age >75 years, Diabetes mellitus, and prior

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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]),[15] CHA_2DS_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).[16] 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.[17]

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.[17] 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.[17] Patient enrollment was consecutive. Patients are being enrolled prospectively into 5 subsequent cohorts, each comprising ≈10 000 patients.[17] 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 (ie, 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 mm Hg.

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_2DS_2-VASc,[9] and modified HAS-BLED (excluding fluctuations in the international normalized ratio) scores, calculated retrospectively from the data provided.[16] 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=10 851; 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 17 184 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 CHA_2DS_2-VASc scores because of their sex. A greater proportion of the women were at moderate-to-high risk of stroke ($CHADS_2$ score of ≥2: 65.1% versus 54.7% of men). Almost all of the women (97.3%) had a CHA_2DS_2-VASc score of ≥2 versus 77.1% of the men. Of the 10 882 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/$P2Y_{12}$ 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 $CHADS_2$ score of 1, men had slightly higher levels of anticoagulant use compared with women. In patients with a $CHADS_2$ 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 $CHADS_2$ 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 (CHA_2DS_2-VASc score of 0) and 41.1% (81/197) of women (CHA_2DS_2-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 (CHA_2DS_2-VASc score of ≥2), 64.6% (4593/7108) of men and 61.6% (4329/7032) of women received an anticoagulant,

Table 1. Global Anticoagulant Registry in the FIELD-Atrial Fibrillation Population by Region and Country (n=17 184)

	Patients Enrolled	
Region/Country	n	%
Asia	3949	23.0
China	946	5.5
India	318	1.9
Japan	827	4.8
Korea	1595	9.3
Singapore	70	0.4
Thailand	193	1.1
Central/South America	1443	8.4
Argentina	306	1.8
Brazil	345	2.0
Chile	181	1.1
Mexico	611	3.6
Europe	10 851	63.1
Austria	271	1.6
Czech Republic	524	3.0
Belgium	403	2.3
Denmark	252	1.5
Finland	216	1.3
France	725	4.2
Germany	1837	10.7
Hungary	340	2.0
Italy	982	5.7
The Netherlands	518	3.0
Norway	117	0.7
Poland	1104	6.4
Russia	526	3.1
Spain	1070	6.2
Sweden	538	3.1
Ukraine	529	3.1
United Kingdom	899	5.2
Other countries	941	5.5
Australia	427	2.5
Canada	348	2.0
South Africa	166	1.0

Table 2. Baseline Characteristics in Men and Women With Nonvalvular Atrial Fibrillation (n=17 184)

Variable	Men (n=9654)	Women (n=7530)
Age		
Mean (SD), y	68/9654 (12)	73/7530 (10)
Age group, n (%)		
<65 y	3560/9654 (36.9)	1550/7530 (20.6)
65–74 y	3144/9654 (32.6)	2400/7530 (31.9)
≥75 y	2950/9654 (30.6)	3580/7530 (47.5)
Body mass index		
Missing data, n (%)	1809 (18.7)	1619 (21.5)
Mean (SD), kg/m^2	27.7 (4.97)	27.8 (5.92)
Current/previous smoker, n (%)	4378/8748 (50.0)	1097/6898 (15.9)
Pulse		
Missing data, n (%)	914 (9.5)	670 (8.9)
Median (IQR), bpm	82.0 (70.0–100.0)	85.0 (70.0–110.0)
Systolic blood pressure		
Missing data, n (%)	667 (6.9)	544 (7.2)
Median (IQR), mm Hg	130.0 (120.0–144.0)	134.0 (120.0–148.0)
Diastolic blood pressure		
Missing data, n (%)	667 (6.9)	544 (7.2)
Median (IQR), mm Hg	80.0 (70.0–89.0)	80.0 (70.0–88.0)
Heavy alcohol consumption, n (%)*	349/8258 (4.2)	28/6494 (0.4)
Medical history, n (%)		
Acute coronary syndromes	1103/9652 (11.4)	520/7527 (6.9)
Bleeding	292/9649 (3.0)	203/7526 (2.7)
Carotid occlusive disease	294/9649 (3.0)	207/7526 (2.8)
Chronic renal disease		
Missing data	2544/7110 (26.4)	1845/5685 (24.5)
Mild renal dysfunction, GFR, 60–89 mL/min	1401/7110 (19.7)	1116/5685 (19.6)
Moderate renal dysfunction, GFR, 30–59 mL/min	754/7110 (10.6)	751/5685 (13.2)
Severe renal dysfunction, GFR, <30 mL/min	133/7110 (1.9)	121/5685 (2.1)
Cirrhosis	63/9648 (0.7)	30/7527 (0.4)
Congestive heart failure	1955/9653 (20.3)	1588/7529 (21.1)
Coronary artery disease	2150/9653 (22.3)	1270/7529 (16.9)
Coronary artery bypass graft surgery	407/8319 (4.9)	100/6425 (1.6)
Diabetes mellitus	2127/9653 (22.0)	1634/7529 (21.7)
Family history of premature cardiac disease†	1666/8008 (20.8)	1379/6219 (22.2)
Hypercholesterolemia	3790/9648 (39.3)	3090/7528 (41.0)
History of hypertension	7303/9653 (75.7)	6114/7529 (81.2)
Left ventricular ejection fraction <40%	734/5638 (13.0)	247/4125 (6.0)
Peripheral artery disease	719/9648 (7.5)	406/7526 (5.4)
Pulmonary embolism or DVT	221/9651 (2.3)	255/7526 (3.4)
Stroke or TIA	1185/9653 (12.3)	993/7529 (13.2)
Stroke	811/9652 (8.4)	640/7526 (8.5)
Systemic embolism	59/9652 (0.6)	52/7525 (0.7)
Other thromboembolism‡	99/9593 (1.0)	81/7470 (1.1)
Hormone replacement therapy	35/9654 (0.4)	119/7530 (1.6)
Risk score		
$CHADS_2$		
Missing data, n (%)	229 (2.4)	128 (1.7)
Mean (SD)	1.8 (1.1)	2.0 (1.1)
Median (IQR)	2.0 (1.0–2.0)	2.0 (1.0–3.0)
0, n (%)	735/9425 (7.8)	383/7352 (5.2)
1, n (%)	3538/9425 (37.5)	2197/7352(29.7)
≥2, n (%)	5152/9425 (54.7)	4822/7352 (65.1)
CHA_2DS_2-VASc		
Missing data, n (%)	281 (2.9)	178 (2.4)
Mean (SD)	2.7 (1.5)	4.0 (1.5)
Median (IQR)	3.0 (2.0–4.0)	4.0 (3.0–5.0)
0, n (%)	381/9373 (4.1)	…
1, n (%)	1769/9373 (18.9)	200/7352 (2.7)
≥2, n (%)	7223/9373 (77.1)	7152/7352 (97.3)
HAS-BLED§		
Missing data, n (%)	3616 (37.5)	2686 (35.7)
Mean (SD)	1.4 (0.9)	1.5 (0.9)
Median (IQR)	1.0 (1.0–2.0)	1.0 (1.0–2.0)
0–2, n (%)	5295/6038 (87.7)	4159/4844 (85.9)
≥3, n (%)	743/6038 (12.3)	685/4844 (14.1)

CHA_2DS_2-VASc indicates cardiac failure or dysfunction, hypertension, age ≥75 [double], diabetes mellitus, stroke [double]-vascular disease, age 65–74, and sex category [female]; $CHADS_2$ 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.

*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.

with or without an antiplatelet, whereas combination therapy with anticoagulant plus antiplatelet was more frequent in men (Figure 2B).

The use of antithrombotic drugs according to bleeding risk stratum is shown in Figure 3. Of the 17 184 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.

Table 3. Use of Antithrombotic Drugs at Diagnosis in Men and Women With Nonvalvular Atrial Fibrillation (n=17 184)

Variable	Men (n=9654)	Women (n=7530)
Antiplatelet, n (%)*		
Aspirin	3279 (34.0)	2357 (31.3)
Adenosine diphosphate receptor or $P2Y_{12}$ inhibitor	772 (8.0)	468 (6.2)
Glycoprotein IIb/IIIa inhibitor (abciximab, eptifibatide, and tirofiban)	29 (0.3)	16 (0.2)
Prostaglandin analog	17 (0.2)	8 (0.1)
Anticoagulant, n (%)*		
Vitamin K antagonist	4867 (50.4)	3770 (50.1)
Factor Xa inhibitor	627 (6.5)	469 (6.2)
Direct thrombin inhibitor	514 (5.3)	411 (5.5)
Heparinoid	97 (1.0)	59 (0.8)
Unfractionated or low-molecular weight heparin	939 (9.7)	776 (10.3)
Other	56 (0.6)	29 (0.4)

*Categories are not mutually exclusive.

The main reasons for not giving an anticoagulant to patients at moderate-to-high risk of stroke ($CHADS_2$ 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 $CHADS_2$ 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.

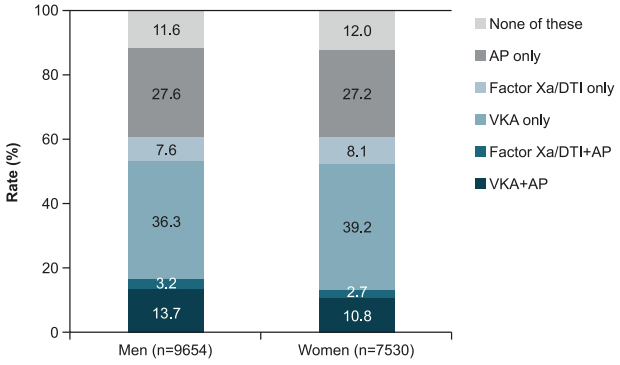

Figure 1. Antithrombotic use (including 460 patients on injectable or undefined factor Xa or direct thrombin inhibitor treatment) for stroke prevention in men and women with nonvalvular atrial fibrillation. AP indicates antiplatelet; DTI, direct thrombin inhibitor; factor Xa, factor Xa inhibitor; and VKA, vitamin K antagonist.

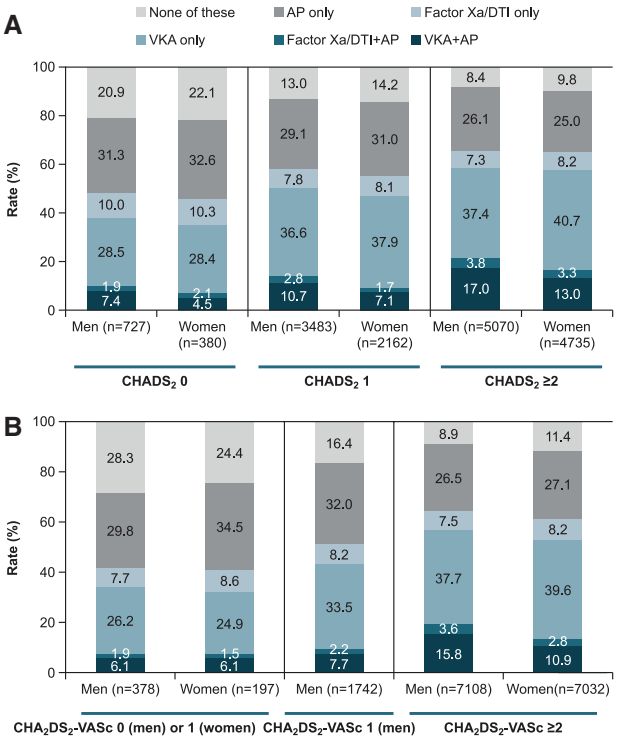

Figure 2. Antithrombotic use (including 460 patients on injectable or undefined factor Xa or direct thrombin inhibitor treatment) for stroke prevention according to (**A**) $CHADS_2$ and (**B**) CHA_2DS_2-VASc scores in men and women with nonvalvular atrial fibrillation. AP indicates antiplatelet; DTI, direct thrombin inhibitor; factor Xa, factor Xa inhibitor; and VKA, vitamin K antagonist.

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 $CHADS_2$ score of 1, women were less likely than men to receive combination antithrombotic therapy. Use of anticoagulants in patients with a $CHADS_2$ score of 0 could reflect suboptimal adherence

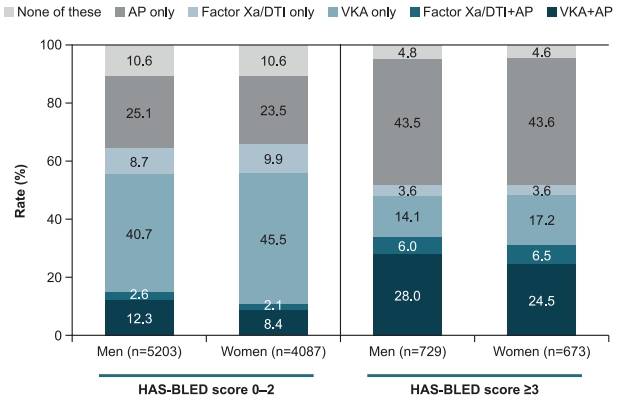

Figure 3. Antithrombotic use (including 460 patients on injectable or undefined factor Xa or direct thrombin inhibitor treatment) according to HAS-BLED score (excluding international normalized ratio fluctuations) in men and women with nonvalvular atrial fibrillation. AP indicates antiplatelet; DTI, direct thrombin inhibitor; factor Xa, factor Xa inhibitor; and VKA, vitamin K antagonist.

Table 4. Main Reasons Why Vitamin K Antagonists Were Not Given to Men and Women With a $CHADS_2$ Score of ≥2 (n=2643)

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

to guidelines, or it may simply indicate that many clinicians think a $CHADS_2$ score of 0 is not low risk[18] and informally consider other risk factors when assessing risk. Among truly low-risk patients (CHA_2DS_2-VASc score of 0 in men and 1 in women), who are not considered candidates for anticoagulant therapy according to the guidelines,[10,12] ≈40% received an anticoagulant. In contrast, among those with a CHA_2DS_2-VASc score of ≥2, in whom anticoagulation is a class I recommendation, one-third did not receive an anticoagulant. Of the women with a CHA_2DS_2-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.[10] The high 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 CHA_2DS_2-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[19–21] 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 at 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 of more intensive therapy in such patients may be somewhat unexpected, given that it is associated with an increased risk of bleeding complications,[22] it probably reflects overlapping risk factors in stroke and bleeding risk scores. The presence of comorbid 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,[10] 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.[23] Hormone replacement therapy may be a risk factor for ischemic stroke.[24] Undertreatment or suboptimal management with an oral anticoagulant is also a possibility, with poor average time in the therapeutic range[25] and frequent interruptions in anticoagulant therapy[8] 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,[26] 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 ($CHADS_2$ 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[27] on stroke prevention, which suggests the use of

Table 5. Use of Anticoagulants in Subgroups With Atrial Fibrillation and $CHADS_2$ Score ≥2: Univariate Analysis (n=9974), where an Odds Ratio of >1 Indicates Higher Probability to Use

		Anticoagulant Use			
Subgroup	Category	%	n	N*	Odds Ratio (95% CI)
Sex	Men (ref.)	66.0	3386	5133	1
	Women	65.7	3147	4791	0.99 (0.91–1.07)
Age group, y	≤55 (ref.)	61.9	340	549	1
	55–65	64.9	922	1420	1.14 (0.93–1.40)
	65–75	67.6	1833	2713	1.28 (1.06–1.55)
	75–85	67.2	2920	4343	1.26 (1.05–1.52)
	>85	57.6	518	899	0.84 (0.67–1.04)
Geographic region	Asia† (ref.)	55.2	1051	1904	1
	Europe‡	69.7	4589	6585	1.87 (1.68–2.07)
	Non-Europe/non-Asia§	62.2	893	1435	1.34 (1.16–1.54)
Previous stroke‖	No (ref.)	65.3	5552	8497	1
	Yes	68.8	979	1424	1.17 (1.03–1.32)
History of hypertension	No (ref.)	69.3	735	1060	1
	Yes	65.4	5798	8864	0.84 (0.73–0.96)
Diabetes mellitus	No (ref.)	65.8	4224	6421	1
	Yes	65.9	2309	3503	1.01 (0.92–1.10)
Vascular disease#	No (ref.)	65.9	5979	9076	1
	Yes	65.3	554	848	0.98 (0.84–1.13)
Congestive heart failure	No (ref.)	66.6	4408	6621	1
	Yes	64.3	2125	3303	0.91 (0.83–0.99)

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.

the CHA_2DS_2-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

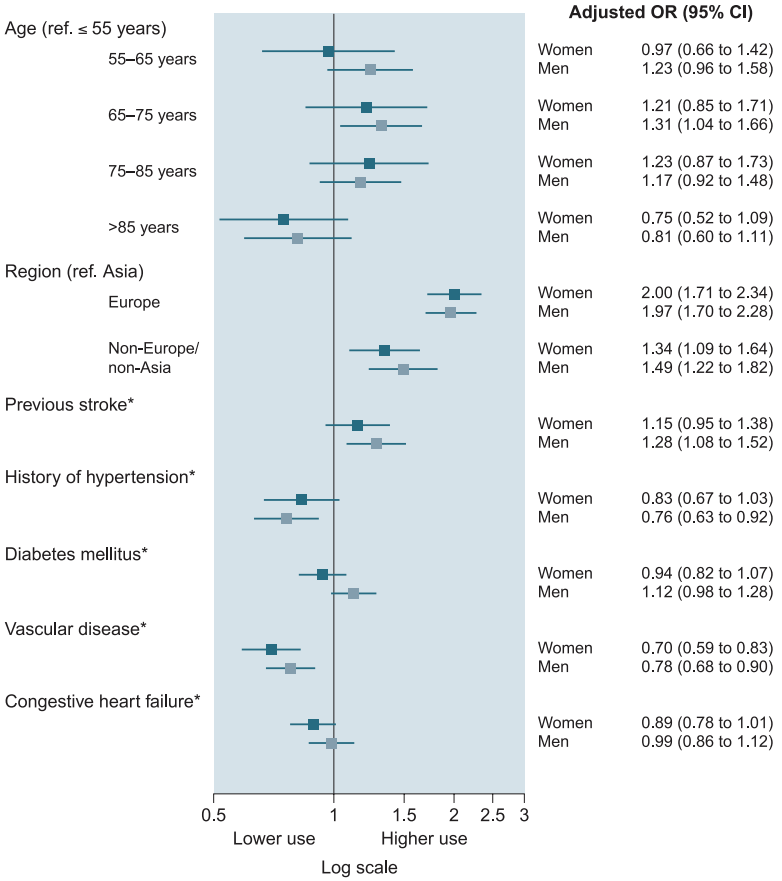

Figure 4. Use of anticoagulants at baseline in subgroups of men and women with a $CHADS_2$ score of ≥2 (n=9974). *Reference group, no history. Fifty patients with missing data on anticoagulant use were removed. Four patients with missing data for independent variables were also removed. Likelihood ratio 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.

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Appendix

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References

1. Volgman AS, Manankil MF, Mookherjee D, Trohman RG. Women with atrial fibrillation: greater risk, less attention. *Gend Med*. 2009;6:419–432. doi: 10.1016/j.genm.2009.09.008.
2. Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. *Eur Heart J*. 2012;33:1500–1510. doi: 10.1093/eurheartj/ehr488.
3. Mikkelsen AP, Lindhardsen J, Lip GY, Gislason GH, Torp-Pedersen C, Olesen JB. Female sex as a risk factor for stroke in atrial fibrillation: a nationwide cohort study. *J Thromb Haemost*. 2012;10:1745–1751. doi: 10.1111/j.1538-7836.2012.04853.x.
4. Friberg J, Scharling H, Gadsbøll N, Truelsen T, Jensen GB; Copenhagen City Heart Study. Comparison of the impact of atrial fibrillation on the risk of stroke and cardiovascular death in women versus men (The Copenhagen City Heart Study). *Am J Cardiol*. 2004;94:889–894. doi: 10.1016/j.amjcard.2004.06.023.
5. Pancholy SB, Sharma PS, Pancholy DS, Patel TM, Callans DJ, Marchlinski FE. Meta-analysis of gender differences in residual stroke risk and major bleeding in patients with nonvalvular atrial fibrillation treated with oral anticoagulants. *Am J Cardiol*. 2014;113:485–490. doi: 10.1016/j.amjcard.2013.10.035.
6. Cove CL, Albert CM, Andreotti F, Badimon L, Van Gelder IC, Hylek EM. Female sex as an independent risk factor for stroke in atrial fibrillation: possible mechanisms. *Thromb Haemost*. 2014;111:385–391. doi: 10.1160/TH13-04-0347.
7. Avgil Tsadok M, Jackevicius CA, Rahme E, Humphries KH, Behlouli H, Pilote L. Sex differences in stroke risk among older patients with recently diagnosed atrial fibrillation. *JAMA*. 2012;307:1952–1958. doi: 10.1001/jama.2012.3490.
8. Gomberg-Maitland M, Wenger NK, Feyzi J, Lengyel M, Volgman AS, Petersen P, Frison L, Halperin JL. Anticoagulation in women with nonvalvular atrial fibrillation in the stroke prevention using an oral thrombin inhibitor (SPORTIF) trials. *Eur Heart J*. 2006;27:1947–1953. doi: 10.1093/eurheartj/ehl103.
9. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest*. 2010;137:263–272. doi: 10.1378/chest.09-1584.
10. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, Hindricks G, Kirchhof P; Guidelines ESCCfP, Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, Document R, Vardas P, Al-Attar N, Alfieri O, Angelini A, Blomstrom-Lundqvist C, Colonna P, De Sutter J, Ernst S, Goette A, Gorenek B, Hatala R, Heidbuchel H, Heldal M, Kristensen SD, Le Heuzey JY, Mavrakis H, Mont L, Filardi PP, Ponikowski P, Prendergast B, Rutten FH, Schotten U, Van Gelder IC, Verheugt FW. 2012 focused update of the ESC guidelines for the management of atrial fibrillation: an update of the 2010 ESC guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J*. 2012; 33:2719–2747.
11. Skanes AC, Healey JS, Cairns JA, Dorian P, Gillis AM, McMurtry MS, Mitchell LB, Verma A, Nattel S; Canadian Cardiovascular Society Atrial Fibrillation Guidelines Committee. Focused 2012 update of the Canadian Cardiovascular Society atrial fibrillation guidelines: recommendations for stroke prevention and rate/rhythm control. *Can J Cardiol*. 2012;28:125–136. doi: 10.1016/j.cjca.2012.01.021.
12. January CT, Wann LS, Alpert JS, Calkins H, Cleveland JC Jr, Cigarroa JE, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the heart rhythm society. *Circulation*. 2014; 130:2071–20104.
13. Mosca L, Barrett-Connor E, Wenger NK. Sex/gender differences in cardiovascular disease prevention: what a difference a decade makes. *Circulation*. 2011;124:2145–2154. doi: 10.1161/CIRCULATIONAHA.110.968792.
14. Kim ES, Menon V. Status of women in cardiovascular clinical trials. *Arterioscler Thromb Vasc Biol*. 2009;29:279–283. doi: 10.1161/ATVBAHA.108.179796.
15. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA*. 2001;285:2864–2870.
16. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest*. 2010;138:1093–1100. doi: 10.1378/chest.10-0134.
17. Kakkar AK, Mueller I, Bassand JP, Fitzmaurice DA, Goldhaber SZ, Goto S, Haas S, Hacke W, Lip GY, Mantovani LG, Verheugt FW, Jamal W, Misselwitz F, Rushton-Smith S, Turpie AG. International longitudinal registry of patients with atrial fibrillation at risk of stroke: Global Anticoagulant Registry in the FIELD (GARFIELD). *Am Heart J*. 2012;163:13–19.e1. doi: 10.1016/j.ahj.2011.09.011.
18. Olesen JB, Fauchier L, Lane DA, Taillandier S, Lip GY. Risk factors for stroke and thromboembolism in relation to age among patients with atrial fibrillation: the Loire Valley Atrial Fibrillation Project. *Chest*. 2012;141:147–153. doi: 10.1378/chest.11-0862.
19. Osseby GV, Benatru I, Sochurkova D, Urbinelli R, Megherbi SE, Couvreur G, Moreau T, Wolf J, Giroud M. Trends in utilization of antithrombotic therapy in patients with atrial fibrillation before stroke onset in a community-based study, from 1985 through 1997. From scientific evidence to practice. *Prev Med*. 2004;38:121–128.
20. Stenestrand U, Lindbäck J, Wallentin L; RIKS-HIA Registry. Anticoagulation therapy in atrial fibrillation in combination with acute myocardial infarction influences long-term outcome: a prospective cohort study from the Register of Information and Knowledge About Swedish Heart Intensive Care Admissions (RIKS-HIA). *Circulation*. 2005;112:3225–3231. doi: 10.1161/CIRCULATIONAHA.105.552984.
21. Nieuwlaat R, Capucci A, Camm AJ, Olsson SB, Andresen D, Davies DW, Cobbe S, Breithardt G, Le Heuzey JY, Prins MH, Lévy S, Crijns HJ; European Heart Survey Investigators. Atrial fibrillation management: a prospective survey in ESC member countries: the Euro Heart Survey on Atrial Fibrillation. *Eur Heart J*. 2005;26:2422–2434. doi: 10.1093/eurheartj/ehi505.
22. Connolly SJ, Pogue J, Hart RG, Hohnloser SH, Pfeffer M, Chrolavicius S, Yusuf S; ACTIVE Investigators. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. *N Engl J Med*. 2009;360:2066–2078. doi: 10.1056/NEJMoa0901301.
23. Friberg L, Benson L, Rosenqvist M, Lip GY. Assessment of female sex as a risk factor in atrial fibrillation in Sweden: nationwide retrospective cohort study. *BMJ*. 2012;344:e3522.
24. Hart RG, Pearce LA, McBride R, Rothbart RM, Asinger RW. Factors associated with ischemic stroke during aspirin therapy in atrial fibrillation: analysis of 2012 participants in the SPAF I-III clinical trials. The Stroke Prevention in Atrial Fibrillation (SPAF) Investigators. *Stroke*. 1999;30:1223–1229.
25. Sullivan RM, Zhang J, Zamba G, Lip GY, Olshansky B. Relation of gender-specific risk of ischemic stroke in patients with atrial fibrillation to differences in warfarin anticoagulation control (from AFFIRM). *Am J Cardiol*. 2012;110:1799–1802. doi: 10.1016/j.amjcard.2012.08.014.
26. Dagres N, Nieuwlaat R, Vardas PE, Andresen D, Lévy S, Cobbe S, Kremastinos DT, Breithardt G, Cokkinos DV, Crijns HJ. Gender-related differences in presentation, treatment, and outcome of patients with atrial fibrillation in Europe: a report from the Euro Heart Survey on Atrial Fibrillation. *J Am Coll Cardiol*. 2007;49:572–577. doi: 10.1016/j.jacc.2006.10.047.
27. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenek B, Heldal M, Hohloser SH, Kolh P, Le Heuzey JY, Ponikowski P, Rutten FH; European Heart Rhythm A, European Association for Cardio-Thoracic Surgery. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J*. 2010; 31:2369–2429.