

Female Sex as a Risk Factor for Ischemic Stroke and Systemic Embolism in Chinese Patients With Atrial Fibrillation: A Report From the China-AF Study

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Background—Previous studies have provided conflicting results as to whether women are at higher risk than men for thromboembolism in the setting of atrial fibrillation (AF). We investigated whether women with AF were at higher risk of ischemic stroke in the China-AF (China Atrial Fibrillation Registry) Study.

Methods and Results—A total of 19 515 patients were prospectively enrolled between August 2011 and December 2016 in the China-AF Study. After exclusion of patients receiving anticoagulation or ablation therapy, 6239 patients (2574 women) with results from at least 6 months of follow-up were used for the analysis. Cox proportional hazards models were performed to evaluate whether female sex was an independent risk factor for thromboembolism after multivariate adjustment. The primary outcome was the time to the first occurrence of ischemic stroke or systemic embolism. After a mean follow-up of 2.81 ± 1.46 years, 152 female patients reached the primary outcome, as compared with 172 male patients. Crude incidence rates of thromboembolism between women and men were of borderline statistical significance (2.08 versus 1.68 per 100 patient-years, $P=0.058$). After multivariable analysis, female sex was not independently associated with an increased thromboembolism risk (hazard ratio 1.09, 95% confidence interval 0.86-1.39). There was no significant difference in thromboembolism risk by sex stratified by age and presence or absence of risk factors (P for interaction all >0.1).

Conclusions—Although crude incidence rates of thromboembolism were higher in Chinese female patients with AF compared with male patients, female sex did not emerge as an independent risk factor for thromboembolism on multivariate analysis.

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Key Words: atrial fibrillation • ischemic stroke • women

Atrial fibrillation (AF) is the most common sustained arrhythmia and is associated with a 5-fold increase in the risk of ischemic stroke.¹ Usually, female AF patients tend to be older, with more comorbidities, and therefore to have a higher incidence of stroke.^{2,3} However, whether female sex is

a prognostic factor for stroke is still uncertain. Large-cohort studies have indicated that women with AF are at 10% to 90% higher risk of stroke than men,^{2,4-8} whereas others failed to find such an association.⁹⁻¹² Notably, the ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) study indicated

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Clinical Perspective

What Is New?

- Our study showed that female sex did not emerge as an independent risk factor for stroke and systemic embolism in Chinese atrial fibrillation patients.
- No significant interactions between sex and age or comorbidities was found for thromboembolism.

What Are the Clinical Implications?

- Our findings do not support consideration of oral anticoagulant treatment for female Chinese patients with a CHA₂DS₂-VASc score of 1.
- Initial decisions on oral anticoagulant treatment guided by a CHA₂DS₂-VA approach (ie, ignoring the Sex category [Sc] criterion) may be appropriate.

that women were at 60% and 80% increased stroke risk than men for those aged ≤ 75 and >75 years respectively,⁴ whereas 3 other studies have reported that female sex is associated with 10% to 23% higher risk of stroke only for patients over the age of 75.⁶⁻⁸ Furthermore, the Danish nationwide cohort study suggested that the excess stroke risk for women was evident among those with ≥ 2 non-sex-related risk factors.¹³ Conversely, a recent Korean nationwide cohort study showed that female patients had a lower risk of ischemic stroke than males.¹⁴ Hence, contemporary European and American AF guidelines are inconsistent in their recommendations as to whether female sex should be used as a risk factor in deciding anticoagulation therapy.^{15,16}

In this study we used data from the China-AF (China Atrial Fibrillation Registry) cohort to evaluate whether women are at higher risk for stroke or systemic embolism (SE) after adjustment of other confounding factors and whether the association is consistent among different subgroups.

Methods

For the concern about intellectual property and patient privacy, the data, analytic methods, and study materials of this study will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Population

The China-AF study is a prospective, multicenter, hospital-based, ongoing registry study of patients diagnosed with AF. The main purpose of this observational study is to understand

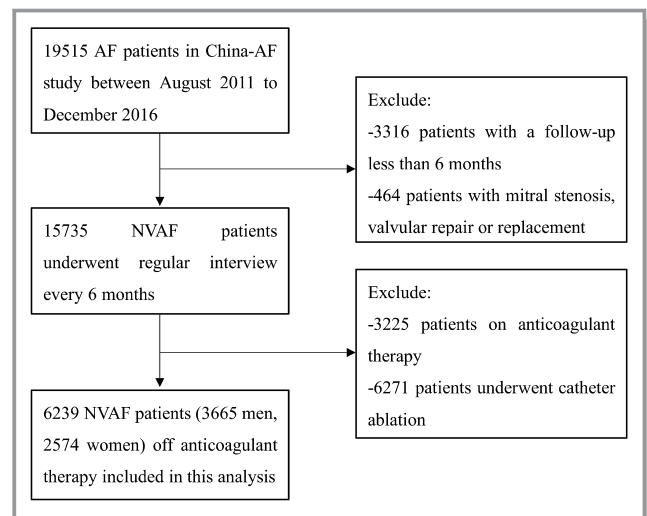


Figure 1. Flowchart of patients included. AF indicates atrial fibrillation; NVAF, nonvalvular atrial fibrillation.

the current clinical practice patterns, prognoses, and related factors in Chinese AF patients and to compare different treatments in real-world practice. Details of the cohort have been described previously.¹⁷ Ethics approval was obtained from the local institutional review board, and written informed consent was obtained from patients. From August 2011 to December 2016, 19 515 AF patients were recruited from outpatient clinics and in-hospital patients of 31 hospitals located in Beijing, China. Patients were followed up at 3 months, 6 months, and every 6 months thereafter. In this analysis we excluded patients with a follow-up of less than 6 months ($n=3316$) and patients with mitral stenosis or valvular repair or replacement ($n=464$). Patients receiving oral anticoagulant treatment at baseline ($n=3225$) were excluded, and we also excluded patients who underwent catheter ablation ($n=6271$) to exclude any possible impact of the procedure on stroke risk.¹⁸⁻²⁰ Finally, 6239 participants were included in this analysis. A flowchart of the study is shown in Figure 1.

Information on patient characteristics, including age, sex, lifestyle factors, type of AF, medical history, medication, education, and insurance, was collected when patients were enrolled. Definitions of each variable were in line with the American College of Cardiology/American Heart Association recommendation on AF clinical data standards and international peer studies.²¹

Follow-Up

Each enrolled patient was followed up at outpatient clinic or through telephone interview every 6 months. Information of medical or interventional therapies, events of incident ischemic stroke/SE, bleedings, hospitalizations, and deaths was collected at each follow-up occasion. Person-time was

censored at the time the patient initiated oral anticoagulant therapy, catheter ablation was applied, first ischemic stroke/SE or death occurred, or the time data were analyzed.

Ascertainment of Thromboembolic Events

The primary outcome was the time to the first occurrence of a thromboembolic event, including ischemic stroke and SE, whichever came first. Patient-reported nonfatal thromboembolic events were adjudicated by 2 independent neurologists separately. Disagreement was resolved by discussion or by involving other senior neurologists.

Definitions

The estimated glomerular filtration rate based on creatinine was calculated with the modified equation for Chinese patients with chronic kidney disease.²² The CHADS₂ score was calculated for each patient by giving 1 point to each patient of age ≥ 75 years, history of hypertension, diabetes mellitus, and congestive heart failure and 2 points to each patient with a history of thromboembolism.²³ We also calculated the CHA₂DS₂-VASc score by giving 2 points to each patient of age ≥ 75 years and a history of thromboembolism and 1 point to each patient of age 65 to 74 years, history of hypertension, diabetes mellitus, congestive heart failure, vascular disease, and female sex.²⁴ A sexless CHA₂DS₂-VASc score (ie, removing female sex), abbreviated as CHA₂DS₂-VA, was calculated by excluding female sex from CHA₂DS₂-VASc score.

Statistical Analyses

Descriptive statistics were used to compare demographic characteristics, comorbid conditions, and concomitant medication between men and women. Continuous variables were presented as mean and standard deviation or median and interquartile range as appropriate. A *t* test or the Wilcoxon rank-sum test was used to compare the differences. Dichotomous variables were presented as percentages and were compared by χ^2 test. Incidence rate of thromboembolic events was reported as the number of events per 100 person-years of follow-up in women and men, respectively. Cumulative incidence rates were estimated with the Kaplan-Meier method and compared with the log-rank test by sex and age groups.

Cox proportional hazards regression was employed to estimate the association between sex and stroke in a series of models with incremental adjustments as follows: model 1 was adjusted for age as a continuous variable; model 2 was adjusted for age, congestive heart failure, hypertension, diabetes mellitus, thromboembolism, and vascular disease; and model 3 was adjusted for all covariates with $P < 0.2$ in the univariate Cox regression model. Results are expressed as

hazard ratios with their 95% confidence intervals (CIs). Interactions between selected variables and sex were tested after multiple adjustment and presented in a forest plot. If covariate data were missing for the Cox regression models, PROC MIANALYZE was used, with a multiple imputation method, to calculate hazard ratios and their 95% CIs and to conduct valid statistical inferences from 5 imputed data sets.

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). All statistical tests were 2-sided; a $P < 0.05$ was considered statistically significant.

Results

We included 2574 women and 3665 men with AF in this analysis: of these, 2576 (41.29%) were identified during hospitalization, 3500 (56.10%) were enrolled from outpatient clinics, and 163 (2.61%) were enrolled from the emergency department. Baseline characteristics of male and female patients were shown in Table 1. Women were generally older (mean age 70.2 years versus 65.8 years, $P < 0.0001$) and were more likely to have a history of heart failure, hypertension, or diabetes mellitus but were less likely to have diagnosed vascular disease than men. Women had higher mean CHADS₂ (2.0 versus 1.7, $P < 0.0001$) and CHA₂DS₂-VASc (3.9 versus 2.4, $P < 0.0001$) scores.

Thromboembolic Events

During a mean follow-up of 2.81 ± 1.46 years, 324 thromboembolic events (291 ischemic strokes and 33 systemic embolisms) occurred. Women accrued 152 thromboembolic events, whereas men accumulated 172 events, with corresponding incidence rates of 2.08 and 1.68 per 100 patient-years, respectively. Crude incidence rates of thromboembolism between women and men were of borderline statistical significance ($P = 0.058$).

Cumulative incidence rates of ischemic stroke/SE subdivided by sex and age groups (< 65 , 65-74, and ≥ 75 years) are shown in Figure 2. On Kaplan-Meier analysis, women were at not at higher risk of stroke/SE than similar-aged men across different age groups.

Women had nonsignificantly different incidences of thromboembolism than men for each CHA₂DS₂-VA score group (Figure 3). The absolute risk of thromboembolism was low among patients with a CHA₂DS₂-VA score of 0, being 0.61, 0.29 per 100 patient-year for women and men ($P = 0.286$), respectively.

Multivariate Analysis

After age had been adjusted as a continuous variable, female sex was still nonsignificantly associated with thromboembolic

Table 1. Baseline Characteristics by Sex

Characteristics	Whole Cohort (N=6239)	Men (N=3665)	Women (N=2574)	P Value
Age, y	67.6±12.6	65.8±13.4	70.2±10.8	<0.0001
BMI, kg/m ²	25.1±3.6	25.2±3.5	25.0±3.8	0.1324
SBP, mm Hg	129.7±17.8	128.6±16.9	131.3±18.8	<0.0001
Pulse pressure, mm Hg	51.9±15.3	50.2±14.6	54.2±15.9	<0.0001
Heart rate, bpm	81.7±21.9	80.8±20.9	82.9±23.2	0.0003
eGFR <60, mL/(min/1.73 m ²)	347/4615 (7.5)	136/2640 (5.2)	211/1975 (10.7)	<0.0001
Echocardiography				
Anteroposterior left atrial diameter, mm	40.6±8.1	41.0±7.9	40.0±8.4	<0.0001
Moderate to severe mitral regurgitation	294/4488 (6.6)	160/2618 (6.1)	134/1870 (7.2)	0.1593
Smoking				
Current	974/6198 (15.7)	903/3639 (24.8)	71/2559 (2.8)	<0.0001
Former	1056/6198 (17.0)	963/3639 (26.5)	93/2559 (3.6)	
Never	4168/6198 (67.2)	1773/3639 (48.7)	2395/2559 (93.6)	
Alcohol use				
Current	1101/6193 (17.8)	1063/3635 (29.2)	38/2558 (1.5)	<0.0001
Former	718/6193 (11.6)	692/3635 (19.0)	26/2558 (1.0)	
Never	4374/6193 (70.6)	1880/3635 (51.7)	2494/2558 (97.5)	
AF type				
Newly diagnosed	852/6236 (13.7)	457/3664 (12.5)	395/2572 (15.4)	0.0006
Paroxysmal	3297/6236 (52.9)	1928/3664 (52.6)	1369/2572 (53.2)	
Persistent	2087/6236 (33.5)	1279/3664 (34.9)	808/2572 (31.4)	
Medical history				
Congestive heart failure	1492/6239 (23.9)	768/3665 (21)	724/2574 (28.1)	<0.0001
Hypertension	4177/6239 (66.9)	2278/3665 (62.2)	1899/2574 (73.8)	<0.0001
Diabetes mellitus	1618/6239 (25.9)	845/3665 (23.1)	773/2574 (30.0)	<0.0001
Thromboembolism	1027/6238 (16.5)	582/3664 (15.9)	445/2574 (17.3)	0.1410
Ischemic stroke	891/6238 (14.3)	505/3664 (13.8)	386/2574 (15.0)	0.1775
Vascular disease	1390/6238 (22.3)	868/3664 (23.7)	522/2574 (20.3)	0.0014
Previous bleeding	325/6237 (5.2)	199/3663 (5.4)	126/2574 (4.9)	0.3470
Hyperlipidemia	1875/6217 (30.2)	979/3652 (26.8)	896/2565 (34.9)	<0.0001
Hypertrophic cardiomyopathy	50/6226 (0.8)	26/3657 (0.7)	24/2569 (0.9)	0.3312
Dilated cardiomyopathy	53/6238 (0.8)	41/3664 (1.1)	12/2574 (0.5)	0.0057
Stroke risk score				
CHADS ₂	1.8±1.5	1.7±1.5	2.0±1.5	<0.0001
CHA ₂ DS ₂ -VASc	3.0±2.0	2.4±1.9	3.9±1.9	<0.0001
Concomitant medication				
Antiplatelet	1674/6239 (26.8)	1010/3665 (27.6)	664/2574 (25.8)	0.1221
Statins	2596/6239 (41.6)	1437/3665 (39.2)	1159/2574 (45.0)	<0.0001
ACEIs/ARBs	2545/6238 (40.8)	1381/3664 (37.7)	1164/2574 (45.2)	<0.0001
Completed high school	1615/5496 (29.4)	1185/3252 (36.4)	430/2244 (19.2)	<0.0001

Continued

Table 1. Continued

Characteristics	Whole Cohort (N=6239)	Men (N=3665)	Women (N=2574)	P Value
Health insurance coverage				
100%	795/6239 (12.7)	517/3665 (14.1)	278/2574 (10.8)	0.0006
Partially	4944/6239 (79.2)	2857/3665 (78.0)	2087/2574 (81.1)	
None	500/6239 (8.0)	291/3665 (7.9)	209/2574 (8.1)	

Data are shown as mean±SD or n/N (%). History of thromboembolism includes ischemic stroke, transient ischemic attack and systemic embolism. Alcohol use is defined as at least 20 g of pure alcohol on 1 occasion for both men and women. Previous bleeding means clinically relevant major or nonmajor bleeding. ACEIs indicates angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ARBs, angiotensin II receptor blockers; BMI, body mass index; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.

risk (hazard ratio 1.06, 95% CI 0.85-1.32, Table 2). The association remained nonsignificant (hazard ratio 1.02, 95% CI 0.82-1.27) even after adjustment for age, history of congestive heart failure, hypertension, diabetes mellitus, thromboembolism, and vascular disease. The results were similar (hazard ratio 1.09, 95% CI 0.86-1.39) when all covariates with $P < 0.2$ in

univariate cox regression model (including age, estimated glomerular filtration rate, left atrial diameter, moderate-to-severe mitral regurgitation, history of congestive heart failure, hypertension, diabetes mellitus, thromboembolism, vascular disease, previous bleeding, use of angiotensin-converting enzyme inhibitor and/or angiotensin II receptor blocker, and

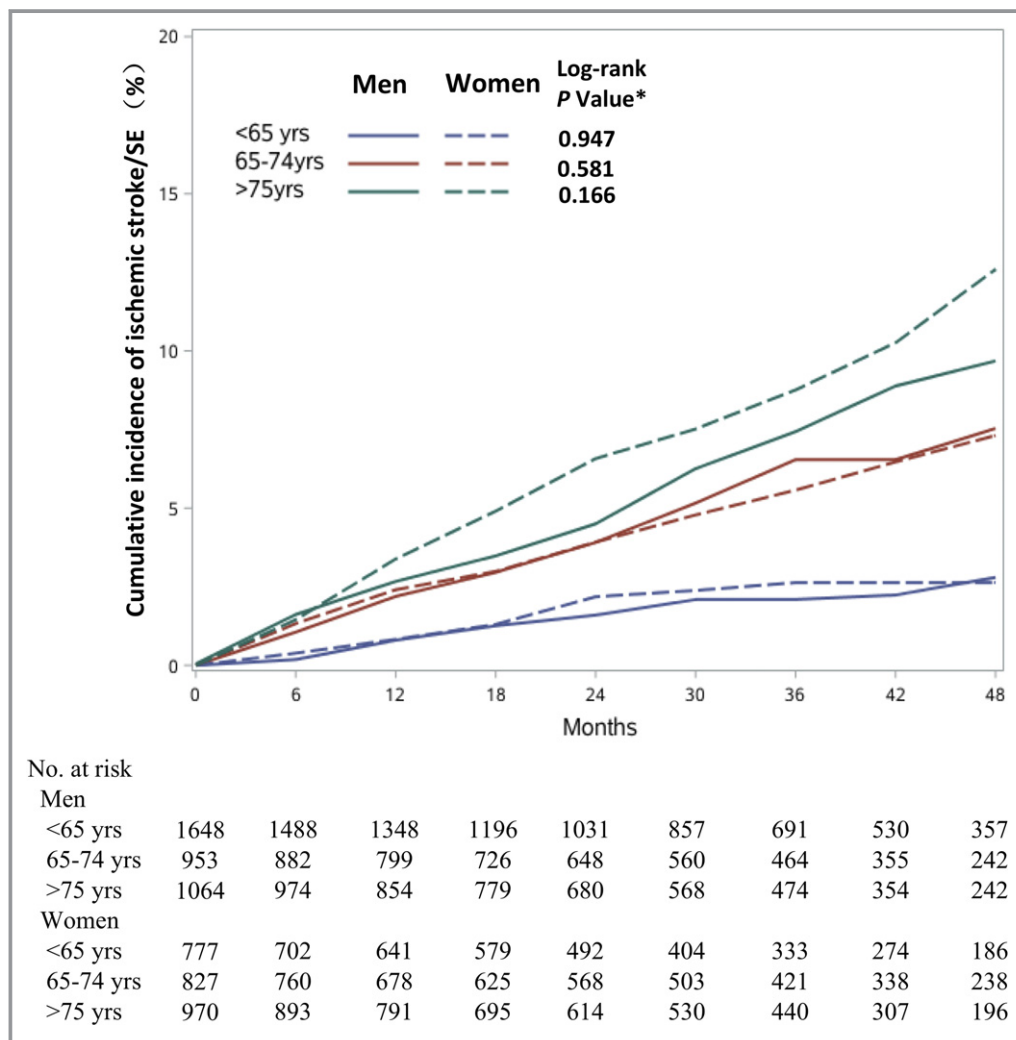


Figure 2. Cumulative incidence rates of ischemic stroke/SE in women and men, stratified by age groups. *Comparisons between men and women, by Log-rank test. SE indicates systemic embolism.

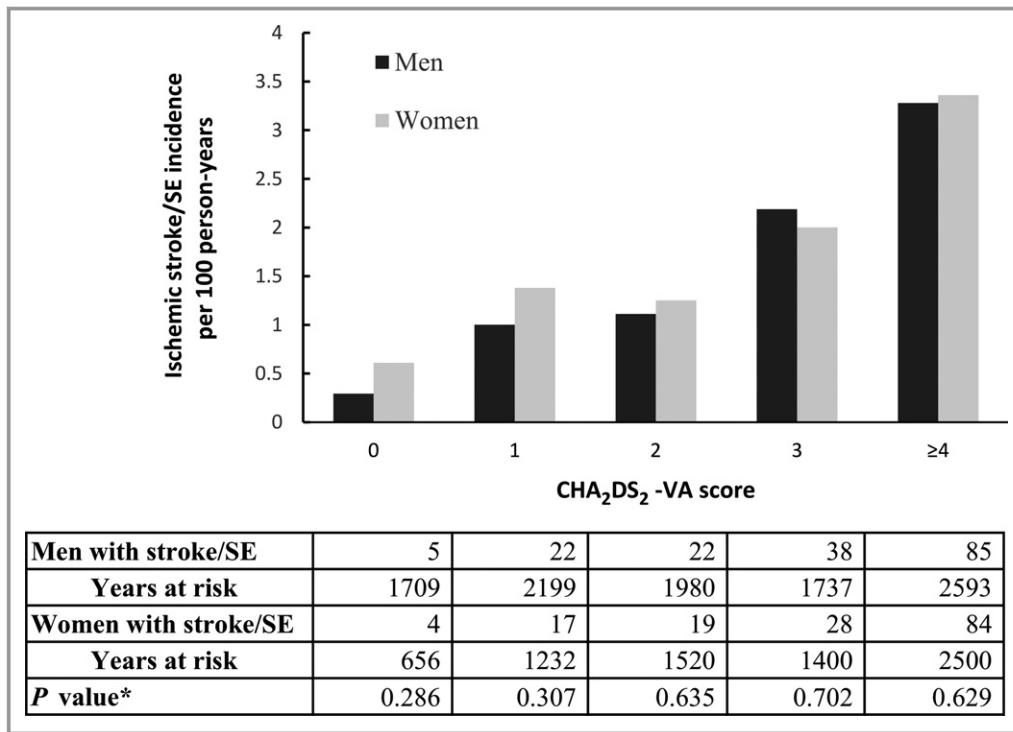


Figure 3. Crude incidence rates of ischemic stroke/SE per 100 person-years by sex according to CHA₂DS₂-VA score. *Comparison between men and women by Fisher exact test. SE indicates systemic embolism.

completion of high school) were adjusted. Table S1 provides all risk estimates of the different covariates included in the univariate and multivariate Cox regression model.

Subgroup Analysis

In subgroups of different age groups (<65, 65-74, and ≥75 years), with and without history of heart failure, hypertension, diabetes mellitus, thromboembolism, as well as vascular diseases, with CHA₂DS₂-VA score ≤1 or ≥2, we found

Table 2. Association Between Female Sex and Incidence of Stroke/SE

	Men	Women
Hazard ratio (unadjusted)	Reference	1.24 (0.99-1.54)
Hazard ratio (adjusted for age*)	Reference	1.06 (0.85-1.32)
Hazard ratio (adjusted for age*, history of heart failure, hypertension, diabetes mellitus, thromboembolism, vascular disease)	Reference	1.02 (0.82-1.27)
Hazard ratio (adjusted for variables with P<0.2 in univariate Cox regression models)	Reference	1.09 (0.86-1.39)

*Age considered as a continuous variable. SE indicates systemic embolism.

no significant interactions between sex and clinically relevant variables (Figure 4).

Discussion

In this large cohort of Chinese patients with AF, we found that although crude annual incidence rates of thromboembolism were higher in Chinese female patients with AF compared with male patients, female sex did not emerge as an independent risk factor for stroke and systemic embolism on multivariate analysis. In addition, no significant interactions between sex and age or comorbidities were found for thromboembolism.

The debate as to whether female sex is an independent risk factor for thromboembolic events in patients with AF remains. The earlier Framingham and ATRIA studies initially reported female sex as a risk factor for stroke.^{4,5} However, these cohorts were conducted in the era of a relatively low awareness of AF and less optimal management of the arrhythmia and associated risk factors. The recognition of AF as a significant clinical condition and improvements in treatment of comorbidities may have contributed to the elimination of sex differences in stroke.

Three more recent large-cohort studies in Canada, Sweden, and Denmark suggested that there was a significant interaction between age and sex for the risk of stroke. Female sex

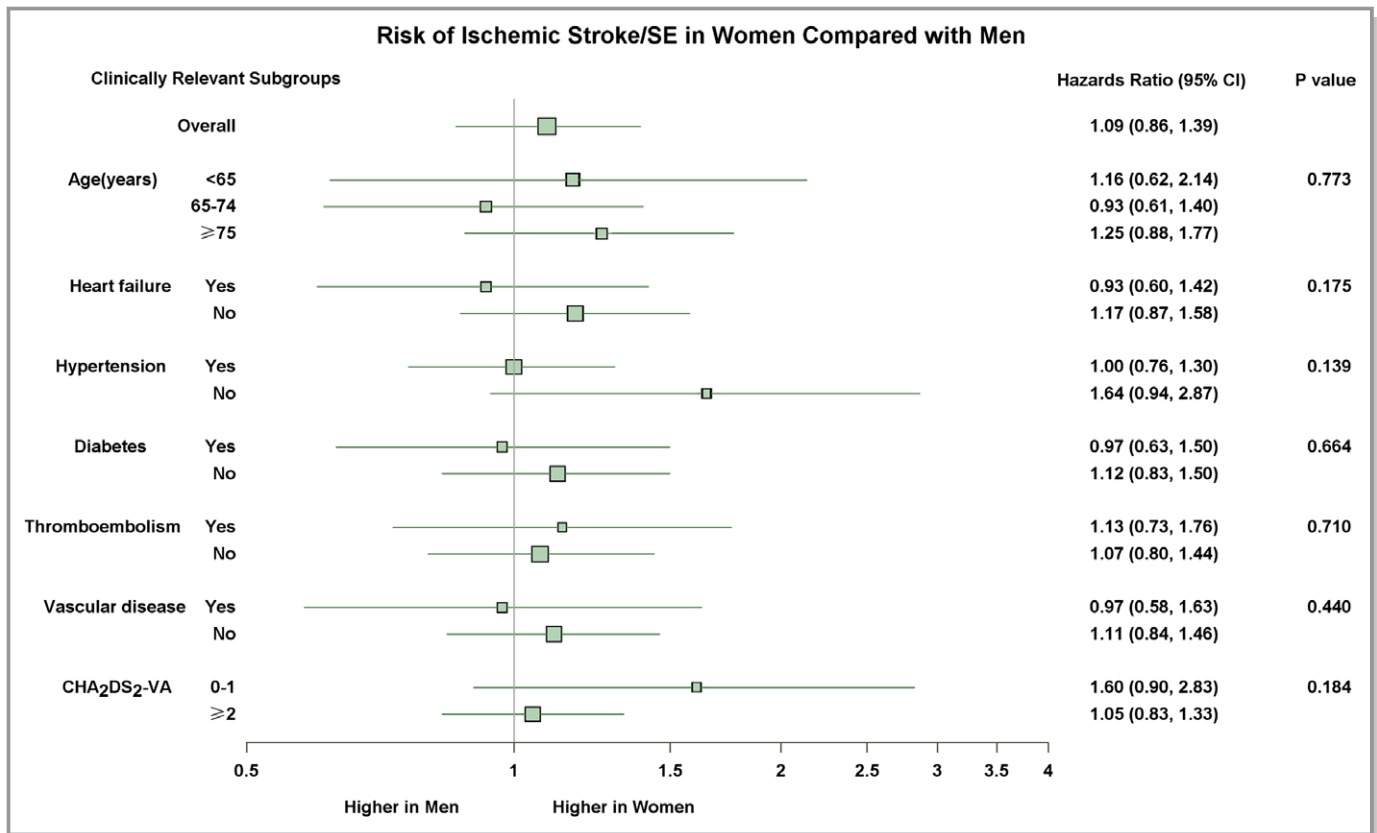


Figure 4. Risk of ischemic stroke/SE in women compared with men in clinically relevant subgroups. All interactions modeled within the previous multivariable Cox regression, except CHA₂DS₂-VA score (in which only sex and CHA₂DS₂-VA score were included in the model). SE indicates systemic embolism.

was a risk factor for stroke only in patients aged ≥ 75 years, not in those aged < 75 years.⁶⁻⁸ However, the Canadian cohort revisited their data recently and found no significant association between female sex and risk of thromboembolism in patients older or younger than 75 years after matching on age and using time-dependent adjustment for confounders.⁹ In addition, the Danish cohort also reviewed their data from 3 nationwide registries recently and showed that female sex had significant interaction with other risk factors and could be considered a risk modifier rather than a risk factor for stroke in patients with AF.¹³ Other analyses based on the UK General Practice Research Database and Asian cohort studies also found no sex differences in stroke risk.^{10,11,14,25,26}

Of note, none of the registry-based studies collected information about lifestyle factors such as smoking, alcohol, and obesity, which may affect the risk of thromboembolic events.²⁷⁻²⁹ The Danish Diet, Cancer and Health study suggested no sex difference in stroke risk after controlling for lifestyle-related factors, including smoking, alcohol, obesity, and hormone replacement therapy.¹² All of these findings suggest that possible unadjusted confounders may contribute to the observed association between female sex and risk of stroke. In our study additional adjustment for echocardiographic,

lifestyle, and socioeconomic factors did not alter the association between female sex and stroke risk.

Our study indicates that female sex is not an independent risk factor for stroke in Chinese AF subjects and should not necessarily be incorporated into their risk stratification for guiding anticoagulation therapy decisions. Current European AF treatment recommendations are the same for female and male patients based on additional risk factors beyond sex.¹⁵ In contrast, American guidelines still provide the possibility of initiating anticoagulation based on female sex alone.¹⁶ However, our findings do not support consideration of oral anticoagulant treatment for female Chinese patients with a CHA₂DS₂-VAsC score of 1, given that these patients displayed an absolute risk of thromboembolism of 0.61 per 100 patient-years.

Contemporary Canadian and Japanese AF guidelines also do not include female sex as a risk factor in considering anticoagulation treatment.^{30,31} Indeed, an analysis from the J-RHYTHM Registry indicated that the CHA₂DS₂-VA score, a risk-scoring system that excludes female sex from CHA₂DS₂-VAsC and performs better in risk stratification for thromboembolic events than the CHA₂DS₂-VAsC score, especially in identifying truly low-risk Japanese AF patients.³² Nonetheless,

the J-RHYTHM registry recorded anticoagulation use only at baseline, and events at follow-up may be confounded by anticoagulation use among high-risk subjects.

Although our findings suggest that female AF patients are not exposed to extra risk of thromboembolic events, it is important to realize that AF was more commonly detected at first stroke in women and was associated with worse stroke outcomes.³³ Women with AF are more likely to be underdiagnosed and managed conservatively. It is reported that women with AF are less likely to receive anticoagulation therapy.³⁴ However, anticoagulant therapy is at least as beneficial in women as in men with AF.³⁵ Specific attention is warranted to promote anticoagulation therapy among women with AF. Indeed, initial decisions on oral anticoagulant treatment could be guided by a CHA₂DS₂-VA score (ie, excluding the sex category criterion), but the Sc risk component may modify and possibly increase stroke risk in women with ≥ 2 additional stroke risk factors.¹³

However, some limitations of the study should be noted. First, the patients in this study were derived from hospitals in Beijing; thus, more symptomatic or sicker patients were possibly more likely to be selected. Also, the numbers of patients and events in our prospective cohort were not comparable with the other nationwide registries. In addition, only information about patient characteristics taken at the baseline was used for the analyses, and hence, the effects of changes in increasing age and incident comorbidities were not taken into consideration.^{36,37} AF categorization in our study did not differentiate permanent AF from persistent AF. Because this categorization applies to both male and female patients, the results are less likely to be impacted by this limitation. Finally, we lacked information about hormone replacement therapy, which may have a role in stroke risk; however, this potential bias is likely to be minimal because the awareness and use of hormone replacement therapy are comparatively low in China.³⁸

Conclusions

Crude incidence rates of thromboembolism were higher in Chinese female patients with AF compared with male patients, but female sex did not emerge as an independent risk factor for stroke and systemic embolism on multivariate analysis. In Chinese AF subjects, initial decisions on oral anticoagulant treatment guided by a CHA₂DS₂-VA approach (ie, ignoring the Sex category [Sc] criterion) may be appropriate.

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Disclosures

Dr Ma received honoraria from Bristol-Myers Squibb, Pfizer, Johnson & Johnson, Boehringer-Ingelheim, and Bayer for delivering lectures. Dr Lip has served as a consultant for Bayer/Janssen, Bristol-Myers Squibb/Pfizer, Boehringer Ingelheim, Novartis, Verseon, and Daiichi-Sankyo and as a speaker for Bayer, Bristol-Myers Squibb/Pfizer, Boehringer Ingelheim, and Daiichi-Sankyo. No fees were directly received personally. Dr Dong also received honoraria from Johnson & Johnson for delivering lectures. The remaining authors have no disclosures to report.

References

1. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke*. 1991;22:983–988.
2. Dagues N, Nieuwlaat R, Vardas PE, Andresen D, Levy S, Cobbe S, Kremastinos DT, Breithardt G, Cokkinos DV, Crijsns 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.
3. Piccini JP, Simon DN, Steinberg BA, Thomas L, Allen LA, Fonarow GC, Gersh B, Hylek E, Kowey PR, Reiffel JA, Naccarelli GV, Chan PS, Spertus JA, Peterson ED; Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) Investigators and Patients. Differences in clinical and functional outcomes of atrial fibrillation in women and men: two-year results from the ORBIT-AF registry. *JAMA Cardiol*. 2016;1:282–291.
4. Fang MC, Singer DE, Chang Y, Hylek EM, Henault LE, Jensvold NG, Go AS. Gender differences in the risk of ischemic stroke and peripheral embolism in atrial fibrillation: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. *Circulation*. 2005;112:1687–1691.
5. Wang TJ, Massaro JM, Levy D, Vasan RS, Wolf PA, D'Agostino RB, Larson MG, Kannel WB, Benjamin EJ. A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the community: the Framingham Heart Study. *JAMA*. 2003;290:1049–1056.
6. 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.
7. 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.
8. 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.
9. Renoux C, Coulombe J, Suissa S. Revisiting sex differences in outcomes in non-valvular atrial fibrillation: a population-based cohort study. *Eur Heart J*. 2017;38:1473–1479.
10. Van Staa TP, Setakis E, Di Tanna GL, Lane DA, Lip GY. A comparison of risk stratification schemes for stroke in 79,884 atrial fibrillation patients in general practice. *J Thromb Haemost*. 2011;9:39–48.
11. Inoue H, Atarashi H, Okumura K, Yamashita T, Origasa H, Kumagai N, Sakurai M, Kawamura Y, Kubota I, Matsumoto K, Kaneko Y, Ogawa S, Aizawa Y, Chinushi M, Kodama I, Watanabe E, Koretsune Y, Okuyama Y, Shimizu A, Igawa O, Bando S, Fukatani M, Saikawa T, Chishaki A. Impact of gender on the prognosis of patients with nonvalvular atrial fibrillation. *Am J Cardiol*. 2014;113:957–962.
12. Overvad TF, Rasmussen LH, Skjoth F, Overvad K, Albertsen IE, Lane DA, Lip GY, Larsen TB. Female sex as a risk factor for thromboembolism and death in

- patients with incident atrial fibrillation. The prospective Danish Diet, Cancer and Health Study. *Thromb Haemost*. 2014;112:789–795.
13. Nielsen PB, Skjoth F, Overvad TF, Larsen TB, Lip GYH. Female sex is a risk modifier rather than a risk factor for stroke in atrial fibrillation: should we use a CHA₂DS₂-VA score rather than CHA₂DS₂-VASc? *Circulation*. 2018;137:832–840.
 14. Kim TH, Yang PS, Uhm JS, Kim JY, Pak HN, Lee MH, Joung B, Lip GYH. CHA₂DS₂-VASc score (congestive heart failure, hypertension, age \geq 75 [doubled], diabetes mellitus, prior stroke or transient ischemic attack [doubled], vascular disease, age 65–74, female) for stroke in Asian patients with atrial fibrillation: a Korean nationwide sample cohort study. *Stroke*. 2017;48:1524–1530.
 15. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, Agewall S, Camm J, Baron Esquivias G, Budts W, Carerj S, Casselman F, Coca A, De Caterina R, Deftereos S, Dobrev D, Ferro JM, Filippatos G, Fitzsimons D, Gorenek B, Guenoun M, Hohnloser SH, Kolh P, Lip GY, Manolis A, McMurray J, Ponikowski P, Rosenhek R, Ruschitzka F, Savelieva I, Sharma S, Suwalski P, Tamargo JL, Taylor CJ, Van Gelder IC, Voors AA, Windecker S, Zamorano JL, Zeppenfeld K. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;37:2893–2962.
 16. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, Conti JB, Ellorin PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW; ACC/AHA Task Force Members. 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:e199–e267.
 17. Du X, Ma C, Wu J, Li S, Ning M, Tang R, Guo X, Long D, Yu R, Sang C, Jiang C, Zhang T, Pan J, Liu X, Dong J, Lip GYH. Rationale and design of the Chinese Atrial Fibrillation Registry Study. *BMC Cardiovasc Disord*. 2016;16:130.
 18. Chang CH, Lin JW, Chiu FC, Caffrey JL, Wu LC, Lai MS. Effect of radiofrequency catheter ablation for atrial fibrillation on morbidity and mortality: a nationwide cohort study and propensity score analysis. *Circ Arrhythm Electrophysiol*. 2014;7:76–82.
 19. Saliba W, Schliamser JE, Lavi I, Barnett-Griness O, Gronich N, Rennert G. Catheter ablation of atrial fibrillation is associated with reduced risk of stroke and mortality: a propensity score-matched analysis. *Heart Rhythm*. 2017;14:635–642.
 20. Friberg L, Tabrizi F, Englund A. Catheter ablation for atrial fibrillation is associated with lower incidence of stroke and death: data from Swedish health registries. *Eur Heart J*. 2016;37:2478–2487.
 21. McNamara RL, Brass LM, Drozda JP Jr, Go AS, Halperin JL, Kerr CR, Levy S, Malenka DJ, Mittal S, Pelosi F Jr, Rosenberg Y, Stryer D, Wyse DG, Radford MJ, Goff DC Jr, Grover FL, Heidenreich PA, Malenka DJ, Peterson ED, Redberg RF; American College of Cardiology/American Heart Association Task Force on Clinical Data Standards, American College of Cardiology, American Heart Association. ACC/AHA key data elements and definitions for measuring the clinical management and outcomes of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on clinical data standards (writing committee to develop data standards on atrial fibrillation). *Circulation*. 2004;109:3223–3243.
 22. Ma YC, Zuo L, Chen JH, Luo Q, Yu XQ, Li Y, Xu JS, Huang SM, Wang LN, Huang W, Wang M, Xu GB, Wang HY. Modified glomerular filtration rate estimating equation for Chinese patients with chronic kidney disease. *J Am Soc Nephrol*. 2006;17:2937–2944.
 23. 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.
 24. 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.
 25. Lin LY, Lee CH, Yu CC, Tsai CT, Lai LP, Hwang JJ, Chen PC, Lin JL. Risk factors and incidence of ischemic stroke in Taiwanese with nonvalvular atrial fibrillation—a nation wide database analysis. *Atherosclerosis*. 2011;217:292–295.
 26. Siu C-W, Lip GYH, Lam K-F, Tse H-F. Risk of stroke and intracranial hemorrhage in 9727 Chinese with atrial fibrillation in Hong Kong. *Heart Rhythm*. 2014;11:1401–1408.
 27. Overvad TF, Rasmussen LH, Skjoth F, Overvad K, Albertsen IE, Lane DA, Lip GY, Larsen TB. Alcohol intake and prognosis of atrial fibrillation. *Heart*. 2013;99:1093–1099.
 28. Overvad TF, Rasmussen LH, Skjoth F, Overvad K, Lip GY, Larsen TB. Body mass index and adverse events in patients with incident atrial fibrillation. *Am J Med*. 2013;126:640.e649–617.
 29. Albertsen IE, Rasmussen LH, Lane DA, Overvad TF, Skjoth F, Overvad K, Lip GY, Larsen TB. The impact of smoking on thromboembolism and mortality in patients with incident atrial fibrillation: insights from the Danish Diet, Cancer, and Health Study. *Chest*. 2014;145:559–566.
 30. JCS Joint Working Group. Guidelines for pharmacotherapy of atrial fibrillation (JCS 2013). *Circ J*. 2014;78:1997–2021.
 31. Macle L, Cairns J, Leblanc K, Tsang T, Skanes A, Cox JL, Healey JS, Bell A, Pilote L, Andrade JG, Mitchell LB, Atzema C, Gladstone D, Sharma M, Verma S, Connolly S, Dorian P, Parkash R, Talajic M, Nattel S, Verma A; CCS Atrial Fibrillation Guidelines Committee. 2016 focused update of the Canadian Cardiovascular Society guidelines for the management of atrial fibrillation. *Can J Cardiol*. 2016;32:1170–1185.
 32. Tomita H, Okumura K, Inoue H, Atarashi H, Yamashita T, Origasa H, Tsuchida E; J-RHYTHM Registry Investigators. Validation of risk scoring system excluding female sex from CHA₂DS₂-VASc in Japanese patients with nonvalvular atrial fibrillation—subanalysis of the J-RHYTHM Registry. *Circ J*. 2015;79:1719–1726.
 33. Edwards JD, Micieli A, Yu AXY, Fang J, Gladstone D. Sex differences in the incidence and outcomes of newly diagnosed atrial fibrillation-related stroke. *Can J Cardiol*. 2018;34:e1–e2.
 34. Hsu JC, Maddox TM, Kennedy K, Katz DF, Marzec LN, Lubitz SA, Gehi AK, Turakhia MP, Marcus GM. Aspirin instead of oral anticoagulant prescription in atrial fibrillation patients at risk for stroke. *J Am Coll Cardiol*. 2016;67:2913–2923.
 35. 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.
 36. Yoon M, Yang PS, Jang E, Yu HT, Kim TH, Uhm JS, Kim JY, Pak HN, Lee MH, Lip GYH, Joung B. Dynamic changes of CHA₂DS₂-VASc score and the risk of ischaemic stroke in Asian patients with atrial fibrillation: a nationwide cohort study. *Thromb Haemost*. 2018;118:1296–1304.
 37. Chao TF, Lip GYH, Liu CJ, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, Liao JN, Chung FP, Chen TJ, Chen SA. Relationship of aging and incident comorbidities to stroke risk in patients with atrial fibrillation. *J Am Coll Cardiol*. 2018;71:122–132.
 38. Jin F, Tao M, Teng Y, Shao H, Li C, Mills E. Knowledge and attitude towards menopause and hormone replacement therapy in Chinese women. *Gynecol Obstet Invest*. 2015;79:40–45.

SUPPLEMENTAL MATERIAL

Table S1. Associations Between Baseline Factors and Ischemic Stroke/SE.

Variable	Univariate Analysis		Multivariate Analysis	
	HR (95%CI)	P value	HR (95%CI)	P value
Sex, female	1.24 (0.99-1.54)	0.058	1.09 (0.86-1.39)	0.482
Age, per year	1.05 (1.04-1.07)	<.0001	1.04 (1.02-1.05)	<.0001
BMI>28kg/m ²	0.83 (0.60-1.15)	0.265	/	/
SBP>140mmHg	1.42 (1.14-1.78)	0.002	/	/
Pulse pressure>60mmHg	1.31 (1.01-1.69)	0.041	/	/
Heart rate>100bpm	1.01 (0.74-1.38)	0.939	/	/
eGFR<60 mL/min/1.73m ²	1.42 (0.92-2.18)	0.110	0.69 (0.43-1.11)	0.129
Left atrial diameter>40mm	1.57 (1.21-2.04)	0.001	1.45 (1.06-2.00)	0.0225
Moderate-to-severe mitral regurgitation	1.44 (0.90-2.31)	0.127	1.07 (0.67-1.72)	0.780
Smoking (any)	0.87 (0.68-1.10)	0.240	/	/
Alcohol use (any)	0.86 (0.67-1.10)	0.220	/	/
Persistent AF	1.15 (0.92-1.44)	0.220	/	/
Medical history				
Heart failure	1.76 (1.39-2.22)	<.0001	1.15 (0.88-1.51)	0.312
Hypertension	1.98 (1.50-2.60)	<.0001	1.48 (1.07-2.04)	0.0168
Diabetes mellitus	1.46 (1.16-1.84)	0.002	1.16 (0.90-1.50)	0.248
Thromboembolism	2.51 (1.98-3.17)	<.0001	2.03 (1.57-2.64)	<.0001
Vascular disease	1.24 (0.96-1.59)	0.097	0.86 (0.65-1.14)	0.307
Previous bleeding	1.97 (1.35-2.86)	<.0001	1.25 (0.81-1.93)	0.308

Hyperlipidemia	1.08 (0.85-1.36)	0.540	/	/
Use of Statins	1.04 (0.84-1.30)	0.706	/	/
Use of ACEIs/ARBs	1.19 (0.95-1.48)	0.127	0.86 (0.67-1.10)	0.228
Completed high school	0.75 (0.57-0.98)	0.032	0.87 (0.66-1.16)	0.344
Health insurance (any)	1.22 (0.79-1.88)	0.363	/	/

BMI, body mass index; SBP, systolic blood pressure; eGFR, estimated glomerular filtration rate; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers.