ORIGINAL RESEARCH

Sex Differences in Oral Anticoagulation and Outcomes of Stroke and Intracranial Bleeding in Newly Diagnosed Atrial Fibrillation

Celina M. Yong, MD, MBA, MSc; Jennifer A. Tremmel, MD, MS; Maarten G. Lansberg, MD, PhD; Jun Fan, MS; Mariam Askari, BS; Mintu P. Turakhia, MD, MAS

BACKGROUND: Female sex is an independent predictor of stroke in patients with atrial fibrillation (AF). Older data suggest undertreatment with anticoagulation among women compared with men. However, it is unknown if novel therapies and updated guidelines have impacted sex differences in AF treatment and outcomes.

METHODS AND RESULTS: We performed a retrospective cohort study of 2.3 million women and men with a new diagnosis of AF and CHA_2DS_2-VASc ≥ 2 from Marketscan US commercial claims data from 2008 to 2015 to determine whether women with AF remain undertreated and whether this difference mediates observed differences in outcomes. There were 358 649 patients with newly diagnosed AF (43% women). Compared with men, women were older, with higher CHA_2DS_2-VASc scores, and higher comorbidity burden ($P<0.0001$ for all). Oral anticoagulation-eligible women with CHA_2DS_2-VASc scores ≥ 2 were more likely to not receive anticoagulation (50.0% women versus 43.9% men). Women, compared with men, had a higher risk of ischemic stroke (adjusted hazard ratio [aHR], 1.27; 95% CI, 1.21–1.32; $P<0.0001$) and hospitalization (aHR, 1.06; 95% CI, 1.05–1.07, $P<0.0001$) but had a lower risk of intracranial bleeding (aHR, 0.91; 95% CI, 0.83–0.99, $P=0.03$). In mediation analysis, nonreceipt of oral anticoagulation partially mediated the observed increased risk of stroke and decreased risk of intracranial bleeding in women.

CONCLUSIONS: In the care of newly diagnosed AF in the United States, women, compared with men, are less likely to receive oral anticoagulation. This appears to mediate the increased risk of both stroke and hospitalization but also appears to mediate lower observed intracranial bleeding risk.

Key Words: anticoagulation ■ atrial fibrillation ■ women

Female sex is an independent predictor of stroke in patients with atrial fibrillation (AF), even among anticoagulated patients.[1–4] Consequently, female sex has been incorporated into risk stratification schemes and clinical guidelines for anticoagulation in AF.[5–7] When vitamin K antagonists were the only oral anticoagulation option for stroke prevention, data suggested undertreatment in women compared with men,[8] even though harms of therapy, such as major

bleeding, were considered comparable.[9] The direct oral anticoagulants (DOACs) have been shown in randomized trials to be at least as effective as warfarin for reduction of stroke but safer than warfarin regarding risk of intracranial hemorrhage (ICH) and, in most cases, all major bleeding.[10–12] Despite relatively rapid diffusion of practice, as well as endorsement of DOACs as first-line therapy in some professional society guidelines,[13] it is not known whether

CLINICAL PERSPECTIVE

What Is New?
- Compared with men, women with newly diagnosed atrial fibrillation were older, with higher CHA_2DS_2-VASc scores and higher comorbidity burden.
- Despite this, women were less likely to receive oral anticoagulation to reduce the risk of stroke, including direct oral anticoagulants.
- Women, compared with men, had a higher risk of ischemic stroke and hospitalization but lower risk of intracranial bleeding.

What Are the Clinical Implications?
- Oral anticoagulation among women partially mediated the observed risk differences by sex in ischemic stroke and hospitalization, suggesting an important target for improving outcomes in women with new atrial fibrillation.

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
DOAC	direct oral anticoagulant
OAC	oral anticoagulant
ICH	intracranial hemorrhage

sex differences persisted after the introduction of DOACs. We therefore sought to determine whether such differences were present and, if so, what factors may be associated with residual sex differences in therapy and outcomes.

METHODS AND RESULTS

We analyzed data from the Truven Health MarketScan Commercials Claims and Encounters and Medicare Supplemental Databases (Truven Health Analytics Inc., Cambridge, MA). The databases capture person-specific clinical use, expenditures, and enrollment across inpatient, outpatient, and prescription drug services. Data are generated from a selection of large employers, health plans, and government and public organizations. Linked and merged data sets that we used in the study include the Inpatient Admissions file, which contains records that summarize information about a hospital admission; the Outpatient Services file, which contains encounters and claims for services from a doctor's office, hospital outpatient facility, emergency

room, or other outpatient facility; and the Outpatient Pharmaceutical Claims File and Enrollment Detail File. This data set has been extensively used for health services and outcomes research in AF and has been used in our prior work.[14,15] This study was approved by the local institutional review board (Stanford, CA) and the Veterans Affairs Research and Development Committee (Palo Alto, CA). Requirement for informed consent was waived.

We included all patients with a primary or secondary inpatient or outpatient diagnosis of AF (*International Classification of Diseases, Ninth Revision [ICD-9]* code 427.31 or 427.32) from 2008 to 2014 (Figure 1). We selected this study period because it captured the period that DOACs were approved for AF and introduced to the market, specifically dabigatran (2010) and rivaroxaban (2011). In addition, patients were required to have no prior AF diagnosis in the previous year, continuous insurance enrollment in the MarketScan databases for at least 6 months before and 1 month after the index AF diagnosis date, a second confirmatory AF diagnosis between 30 and 365 days of the new AF diagnosis, and any outpatient medication within 90 days of the first AF diagnosis. The rationale is to increase specificity for AF in the cohort, minimize "rule-out" diagnoses, and identify patients who continued to use the Veterans Affairs system for subsequent care. We have previously used this approach for prior claims-cohort studies.[16,17]

Primary Predictor and Outcomes

The primary predictor was patient sex, obtained from claims data enrollment records. The primary outcome was outpatient drug receipt of any oral anticoagulant (OAC) and any DOAC (dabigatran, rivaroxaban, or apixaban; we did not evaluate edoxaban because the drug was not approved or available in the United States during the observation period). We also assessed time to clinical outcomes of ischemic stroke, intracerebral hemorrhage, and all-cause hospitalization.

Clinical Covariates

Baseline comorbidities (cardiovascular and noncardiovascular) were determined using comorbidity-specific *ICD-9* codes from up to 1 year before the new AF date based on our previous work.[18] We assessed comorbidities using the Charlson and Selim Comorbidity Indices and assessed stroke risk using the CHA_2DS_2 and CHA_2DS_2-VASc scores. Modified HAS-BLED bleeding risk score, which takes into account hypertension, abnormal renal/liver function, stroke, bleeding, elderly age, and drugs/alcohol, was calculated as a measure of baseline bleeding risk.
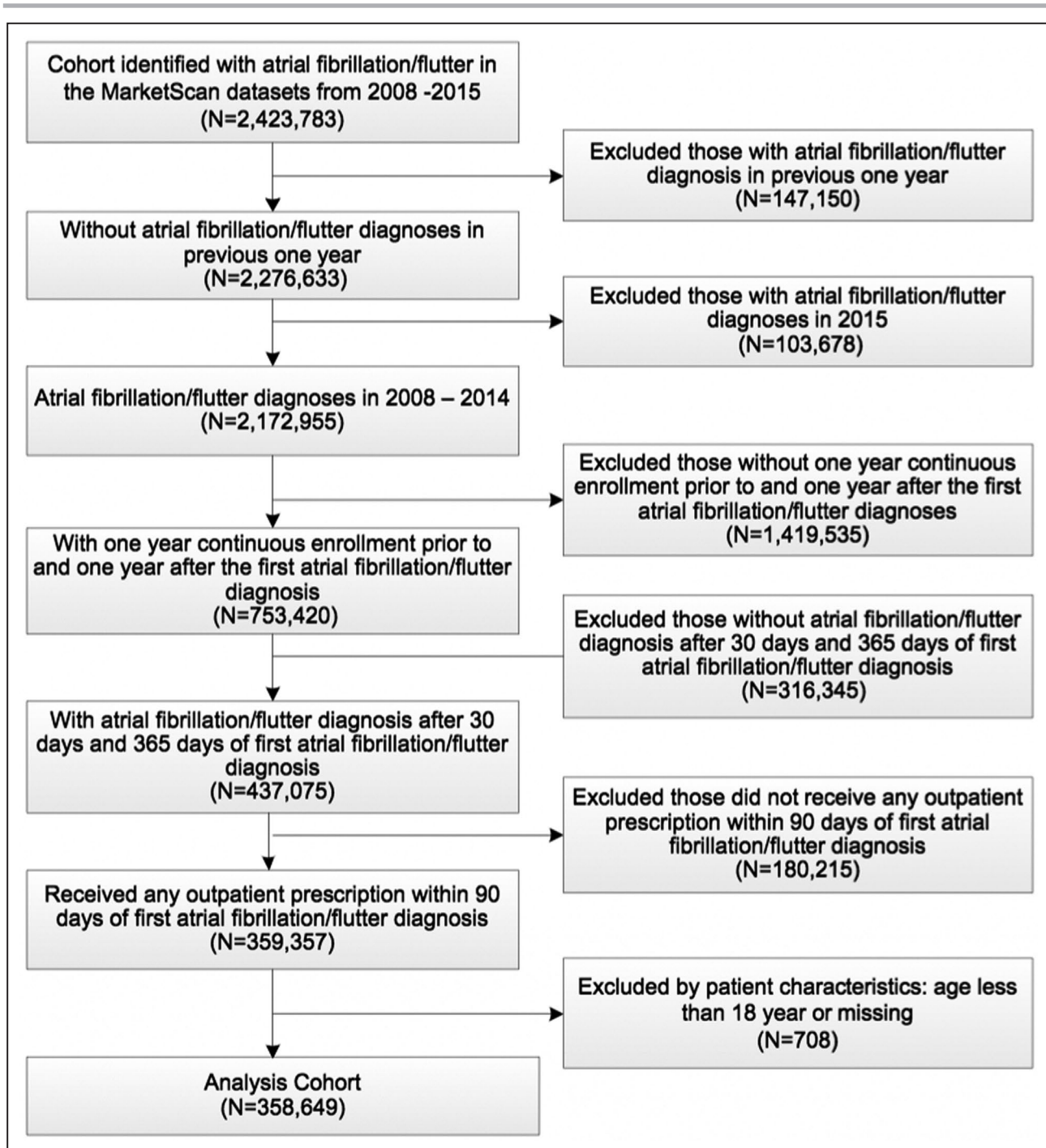
Cohort identified with atrial fibrillation/flutter in the MarketScan datasets from 2008 -2015 (N=2,423,783)

Excluded those with atrial fibrillation/flutter diagnosis in previous one year (N=147,150)

Without atrial fibrillation/flutter diagnoses in previous one year (N=2,276,633)

Excluded those with atrial fibrillation/flutter diagnoses in 2015 (N=103,678)

Atrial fibrillation/flutter diagnoses in 2008 – 2014 (N=2,172,955)

Excluded those without one year continuous enrollment prior to and one year after the first atrial fibrillation/flutter diagnoses (N=1,419,535)

With one year continuous enrollment prior to and one year after the first atrial fibrillation/flutter diagnosis (N=753,420)

Excluded those without atrial fibrillation/flutter diagnosis after 30 days and 365 days of first atrial fibrillation/flutter diagnosis (N=316,345)

With atrial fibrillation/flutter diagnosis after 30 days and 365 days of first atrial fibrillation/flutter diagnosis (N=437,075)

Excluded those did not receive any outpatient prescription within 90 days of first atrial fibrillation/flutter diagnosis (N=180,215)

Received any outpatient prescription within 90 days of first atrial fibrillation/flutter diagnosis (N=359,357)

Excluded by patient characteristics: age less than 18 year or missing (N=708)

Analysis Cohort (N=358,649)

Figure 1. Cohort inclusion criteria.
Final analysis cohort included 358 649 patients.

Statistical Analysis

We compared sex differences in baseline characteristics using a chi-square test for categorical variables and a Student t test for continuous variables. Univariable and multivariable Cox proportional hazards regression were used to examine the association between sex and OAC drug receipt, type of OAC, and each clinical outcome. In the multivariable model, we adjusted for age, region, insurance plan,[19] Charlson Comorbidity Index score, congestive heart failure, hypertension, diabetes mellitus, and baseline medications. Logistic regression was conducted to test if anticoagulation drug receipt within 30 days before and up to 90 days following a new AF diagnosis mediated the effect of sex differences in outcomes. Given that indirect effects can work

Table 1. Baseline Characteristics

	All Patients (N=358 649)	Male (N=205 756)	Female (N=152 893)	P Value
Female, %	43			
Male, %	57			
Age, y	66.2±13.4	64.2±13.2	68.9±13.3	<0.0001
Charlson Comorbidity Index	1.4±1.5	1.4±1.5	1.4±1.4	0.49
Selim Comorbidity Index	3.6±2.7	3.5±2.7	3.8±2.7	<0.0001
CHADS$_2$ score	1.4±1.2	1.3±1.2	1.5±1.2	<0.0001
CHA$_2$DS$_2$-VASc score	2.7±1.8	2.1±1.7	3.4±1.6	<0.0001
HAS-BLED score	1.7±1.2	1.6±1.2	1.8±1.2	<0.0001
Disease, n (%)				
Congestive heart failure	79 966 (22.3)	46 164 (22.4)	33 802 (22.1)	0.02
Hypertension	225 298 (62.8)	125 118 (60.8)	100 180 (65.5)	<0.0001
Diabetes mellitus	103 167 (28.8)	62 465 (30.4)	40 702 (26.6)	<0.0001
Prior stroke/transient ischemic attack	23 766 (6.6)	11 837 (5.8)	11 929 (7.8)	<0.0001
Prior myocardial infarction	21 239 (5.9)	13 992 (6.8)	7247 (4.7)	<0.0001
Anemia	50 944 (14.2)	25 841 (12.6)	25 103 (16.4)	<0.0001
Prior bleeding	38 273 (10.7)	22 380 (10.9)	15 893 (10.4)	<0.0001
Peripheral artery disease	28 378 (7.9)	16 015 (7.9)	12 363 (8.1)	0.0009
Chronic kidney disease	44 036 (12.3)	26 010 (12.6)	18 026 (11.8)	<0.0001
Region, n (%)				<0.0001
Northeast	67 105 (18.7)	38 312 (18.6)	28 793 (18.8)	
North Central	113 898 (31.8)	64 019 (31.1)	49 879 (32.6)	
South	114 281 (31.9)	66 328 (32.2)	47 953 (31.4)	
West	60 692 (16.9)	35 444 (17.2)	25 248 (16.5)	
Unknown	2673 (0.8)	1653 (0.8)	1020 (0.7)	
Insurance plan type, n (%)				<0.0001
Comprehensive	110 584 (30.8)	56 998 (27.7)	53 586 (35.1)	
EPO	1534 (0.4)	1084 (0.5)	450 (0.3)	
HMO	44 510 (12.4)	25 692 (12.5)	18 818 (12.3)	
POS	18 463 (5.2)	11 122 (5.4)	7341 (4.8)	
PPO	163 913 (45.7)	98 237 (47.7)	65 676 (43.0)	
POS with capitation	887 (0.3)	610 (0.3)	277 (0.2)	
CDHP	7212 (2.0)	4708 (2.3)	2504 (1.6)	
HDHP	2897 (0.8)	2025 (1.0)	872 (0.6)	
Missing	8649 (2.4)	5280 (2.6)	3369 (2.2)	
Baseline medications				
Cardiovascular medications, n (%)				
Aspirin	3608 (1.0)	1835 (0.9)	1773 (1.2)	<0.0001
Warfarin	49 927 (13.9)	29 061 (14.1)	20 866 (13.7)	<0.0001
Dabigatran	1817 (0.5)	1153 (0.6)	664 (0.4)	<0.0001
Rivaroxaban	1182 (0.3)	663 (0.3)	519 (0.3)	0.37
Clopidogrel	34 498 (9.6)	21 707 (10.6)	12 791 (8.4)	<0.0001
Apixaban	160	97	63	<0.0001
	(0.04)	(0.05)	(0.04)	
Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers	181 621 (50.6)	102 646 (49.9)	78 975 (51.7)	<0.0001
Diuretics	142 564 (35.5)	72 997 (35.5)	69 567 (45.5)	<0.0001
Niacin or fibrates	14 101 (3.9)	10 576 (5.1)	3525 (2.3)	<0.0001
Statins	148 140 (43.5)	89 477 (43.5)	58 663 (38.4)	<0.0001

(*Continued*)

Table 1. Continued

	All Patients (N=358 649)	Male (N=205 756)	Female (N=152 893)	P Value
Antiarrhythmic drugs, n (%)				
All Class I	14 759 (4.1)	6555 (3.2)	8204 (5.4)	<0.0001
Class III (sotalol/dofetilide)	5757 (1.6)	3457 (1.7)	2300 (1.5)	<0.0001
Amiodarone	9186 (2.6)	5934 (2.9)	3252 (2.1)	<0.0001
Rate-controlling drugs, n (%)				
Metoprolol	80 532 (22.5)	44 469 (21.6)	36 063 (23.6)	<0.0001
Carvedilol	27 928 (7.8)	18 250 (8.9)	9678 (6.3)	<0.0001
Atenolol	33 071 (9.2)	16 954 (8.2%)	16 117 (10.5%)	<0.0001
		(8.2)	(10.5)	
Calcium channel blockers, n (%)				
Diltiazem	20 404 (5.7)	9736 (4.7)	10 668 (7.0)	<0.0001
Verapamil	7829 (2.2)	3622 (1.8)	4207 (2.8)	<0.0001

CDHP indicates consumer-directed health plan; EPO, exclusive provider organization; HDHP, high-deductible health plan; HMO, health maintenance organization; POS, point of service; and PPO, preferred provider organization.

through a mediator of interest, we performed mediation analysis, using multivariable logistic regression, to determine whether the association of sex on clinical outcomes was mediated by anticoagulation. Mediation was assessed for in a stepwise fashion using the Baron and Kenny approach.[20,21] All analyses were performed using SAS, version 9.1 (Cary, NC) and STATA, version 11.0 (College Station, TX).

We identified 358 649 patients meeting our cohort inclusion and exclusion criteria (age 66.2±13.4; 43% women; CHA_2DS_2-VASc score 2.7±1.8). Analysis of baseline characteristics (Table 1) demonstrated that, compared with men, women were older and had higher CHA_2DS_2VASc scores and higher Selim comorbidity indices. More women had a history of hypertension, stroke, and anemia, but fewer women had a history of diabetes mellitus and myocardial infarction compared with men. We found baseline sex differences in prescription of antiarrhythmic drugs, with more women prescribed antiarrhythmics than

men (9.0% women versus 7.7% men, $P<0.0001$), and more women also on rate-controlling medications than men (40.5% women versus 38.7% men, $P<0.0001$).

Overall, women had a lower prevalence of OAC drug receipt in the 90 days following a new AF diagnosis (warfarin [38.1% women versus 41.1% men; $P<0.0001$] and any DOAC [11.9% women versus 14.4% men; $P<0.0001$]) compared with men (Table 2). When we restricted the population to anticoagulation-eligible patients with low bleeding risk (CHA_2DS_2VASc score of ≥2 and HAS-BLED score of ≤3), these differences persisted for warfarin receipt (40.4% women versus 45.7% men; $P<0.0001$) and DOAC receipt (13.0% women versus 14.5% men; $P<0.0001$). When restricting even further to only high-risk patients with a CHA_2DS_2VASc score of ≥4, we found that women were still less likely than men to receive any form of anticoagulation (49.0% women versus 53.0% men; $P<0.0001$). The odds ratio for

Table 2. Anticoagulation by Sex and CHA_2DS_2-VASC and HAS-BLED Scores

Medication(s)	All Patients (N=358 649) , n (%)	Male (N=205 756) , n (%)	Female (N=87 581) , n (%)	P Value	Anticoagulation-Eligible Patients* (N=226 94)9, n (%)	Male (N=107 439) , n (%)	Female (N =119 510) , n (%)	P Value
No anticoagulation	176 239 (49.1)	96 424 (46.9)	79 815 (52.2)	<0.0001	105 255 (46.4)	46 121 (42.9)	59 134 (49.5)	<0.0001
Any anticoagulation	182 410 (50.9)	109 332 (53.1)	73 078 (47.8)	<0.0001	121 694 (53.6)	61 318 (57.1)	60 376 (50.5)	<0.0001
Warfarin	142 868 (39.8)	84 637 (41.1)	58 231 (38.1)	<0.0001	97 374 (42.9)	49 130 (45.7)	48 244 (40.4)	<0.0001
Direct oral anticoagulants	49 193 (13.7)	30 318 (14.8)	18 875 (12.4)	<0.0001	31 034 (13.9)	15 545 (14.5)	15 489 (13)	<0.0001
Dabigatran	22 057 (6.2)	14 017 (6.8)	8040 (5.3)	<0.0001	13 775 (6.1)	7163 (6.7)	6612 (5.5)	<0.0001
Rivaroxaban	20 587 (5.7)	12 466 (6.1)	8121 (5.3)	<0.0001	12 946 (5.9)	6301 (5.9)	6645 (5.6)	0.0018
Apixaban	6549 (1.8)	3835 (1.9)	2714 (1.8)	0.05	4313 (1.9)	2081 (1.9)	2232 (1.9)	0.23

*Anticoagulation eligible defined as CHA_2DS_2Vasc Score≥2 and HAS-BLED score ≤3.

Table 3. Primary Outcomes (N=358 649)

Outcomes	Sex	Patients, N	Events, N (%)	Unadjusted Incidence Rate (per 1000 person-years)	Unadjusted Hazard Ratio* (95% CI)	P Value	Adjusted Hazard Ratio*,† (95% CI)	P Value
All-cause hospitalization	Female	152 893	93 068 (60.9)	344.7 (342.5–346.9)	1.14 (1.13–1.15)	<0.001	1.06 (1.05–1.07)	<0.0001
	Male	205 756	115 558 (56.2)	297.9 (296.2–299.6)				
Stroke	Female	152 893	5114 (3.3)	10.9 (10.6–11.2)	1.52 (1.46–1.59)	<0.0001	1.27 (1.21–1.32)	<0.0001
	Male	205 756	4574 (2.2)	7.2 (7.0–7.4)				
ICH	Female	152 893	921 (0.6)	1.9 (1.8–2.1)	1.04 (0.95–1.13)	0.39	0.91 (0.83–0.99)	0.03
	Male	205 756	1189 (0.6)	1.8 (1.7–2.0)				

ICH indicates intracranial hemorrhage.

*Reference group is male.

†Adjusted for age, Charlson Comorbidity Index score, congestive heart failure, hypertension, diabetes mellitus, region, insurance plan, and receipt of concomitant drug therapies (antiplatelet agent, angiotensin-converting enzyme/angiotensin receptor blocker, stain, niacin/fibrate).

the association between female sex with no anticoagulation was 1.24 (95% CI, 1.22–1.26; $P<0.0001$) unadjusted and 1.20 (95% CI, 1.18–1.22; $P<0.0001$) adjusted, with similar significant findings among the subgroup of anticoagulation-eligible patients.

Women, compared with men, experienced higher risk of ischemic stroke and all-cause hospitalization (Table 3). After adjustment for age, Charlson Comorbidity Index score, heart failure, hypertension, diabetes mellitus, geographic region, insurance plan, and receipt of concomitant drug therapies, female sex remained associated with a higher risk of stroke (hazard ratio [HR], 1.27; 95% CI, 1.21–1.32; $P<0.0001$) and all-cause hospitalization (HR, 1.06; 95% CI, 1.05–1.07; $P<0.0001$) (Table 3). There was a modest decreased association of ICH after adjustment (HR, 0.91; 95% CI, 0.83–0.99; $P=0.03$). Kaplan–Meier curves for ischemic stroke demonstrate the lower survival curve for women compared with men, shown in Figure S1.

For our mediation analysis limited to those with CHA_2DS_2VASc score of ≥2, there was evidence of partial mediation by anticoagulant drug receipt for ischemic stroke (indirect effect, 0.089; 95% CI, 0.86–0.93; $P<0.0001$) and all-cause hospitalization (indirect effect, 1.021; 95% CI, 1.004–1.037; $P=0.014$) (Figure 2). Anticoagulation also partially mediated ICH (indirect effect, 1.41; 95% CI, 1.28–1.55; $P<0.0001$) (Figure 2), although the absolute risk was small and comparable with men.

DISCUSSION

In summary, we found that in a contemporary cohort of US patients with commercial health insurance, women are less likely to be prescribed oral anticoagulation, especially a DOAC. Women with AF also experience higher risk of ischemic stroke and all-cause hospitalization, yet lower risk of ICH compared with men. Importantly, anticoagulation differences in men and

women statistically mediate the observed differences in stroke and all-cause hospitalization but do not explain the differences completely. Not surprisingly, OAC also mediates the risk of ICH in women.

There are a variety of reasons that may explain why women are less likely to be prescribed oral anticoagulation. First, despite recent evidence suggesting an overall higher risk profile of women for stroke in AF and updated guidelines with integration of sex into the CHA_2DS_2-VASc score, clinicians may subscribe to more recent registry data demonstrating that sex may be more of a risk modifier than a risk factor, especially at lower risk scores.[22] However, in our subanalysis limited to only high-stroke-risk patients, in which sex would be expected to play a more important role as a modifier, we found that the same sex differences persisted regardless of overall number of risk factors, with women consistently receiving less anticoagulation than men regardless of risk. Alternatively, clinicians may be downplaying the risk in women for similar reasons that risk for heart disease among women is not fully appreciated, resulting in lower anticoagulation prescriptions for women.[23] Additionally, women may decide against anticoagulation therapy on the basis of the kind of shared decision-making support and risk framing experienced by them. Gender concordance between patient and providers has shown to result in improved patient survival in cardiac patients,[24] but 88% of cardiologists and 96% of electrophysiologists are men.[25] Patient nonmedical factors, such as time and cost, may also impact ability to treat AF effectively among women.[26] For example, women are more likely than men to delay care because of logistical barriers,[26] which may translate into lower compliance with time-intensive International Normalized Ratio monitoring required when taking warfarin. A better understanding of these issues may help us identify missed opportunities to close gender gaps in anticoagulation, such as through the increased

				OR	P	Mediation Yes/No
Logistic Regression Outcome (Y): stroke						
Step1	$Y = B_0 + B_1X + e$	(diagram: c, X → Y)	X: sex	1.259 (1.205-1.315)	<.0001	
Step2	$M = B_0 + B_1X + e.$	(diagram: X —a→ M)	M: OAC use X: sex	0.782 (0.770-0.795)	<.0001	
Step3	$Y = B_0 + B_1M + e$	(diagram: M —b→ Y)	M: OAC use Y: stroke	0.882 (0.844-0.920)	<.0001	Yes, partial mediation
Step4	$Y = B_0 + B_1X + B_2M + e$	(diagram: c', X, M —b→ Y)	Y:stroke X:sex	1.250 (1.197-1.306)	<.0001	
			M:OAC use	0.894 (0.856-0.933)	<.0001	

				OR	P	Mediation Yes/No
Logistic Regression Outcome (Y): all cause hospitalization						
Step1	$Y = B_0 + B_1X + e$	(diagram: c, X → Y)	X: sex	0.960 (0.944-0.975)	<.0001	
Step2	$M = B_0 + B_1X + e.$	(diagram: X —a→ M)	M: OAC use X: sex	0.782 (0.770-0.795)	<.0001	
Step3	$Y = B_0 + B_1M + e$	(diagram: M —b→ Y)	M: OAC use Y: all cause hospitalization	1.023 (1.007-1.040)	0.0059	Yes, partial mediation
Step4	$Y = B_0 + B_1X + B_2M + e$	(diagram: c', X, M —b→ Y)	Y: all cause hospitalization X: sex	0.961 (0.945-0.977)	<.0001	
			M: OAC use	1.021 (1.004-1.037)	0.0142	

				OR	P	Mediation Yes/No
Logistic Regression Outcome (Y): ICH						
Step1	$Y = B_0 + B_1X + e$	(diagram: c, X → Y)	X: sex	0.866 (0.790-0.950)	0.0023	
Step2	$M = B_0 + B_1X + e.$	(diagram: X —a→ M)	M: OAC use X: sex	0.782 (0.770-0.795)	<.0001	
Step3	$Y = B_0 + B_1M + e$	(diagram: M —b→ Y)	M: OAC use Y: ICH	1.418 (1.290-1.559)	<.0001	Yes, partial mediation
Step4	$Y = B_0 + B_1X + B_2M + e$	(diagram: c', X, M —b→ Y)	M:OAC use Y:ICH	0.884 (0.806-0.970)	0.009	
			X:sex	1.407 (1.280-1.547)	<.0001	

Figure 2. Mediation of sex differences in outcomes by OAC use.
OAC use partially mediates gender differences in all-cause hospitalization, stroke, and ICH for the cohort with CHA$_2$DS$_2$VASc score ≥2. ICH indicates intracerebral hemorrhage; and OAC, oral anticoagulant.

prescription of DOACs, which have no laboratory monitoring requirements.

Our findings demonstrating lower anticoagulation with DOACs among women support older findings from North America (US Medicare population and a Canadian study).[27–29] The more recent PINNACLE (https://cvquality.acc.org/NCDR-home/registries/outpatient-registries/pinnacle-registry) Registry of US ambulatory encounters also demonstrated lower DOAC use among women.[30] Our findings importantly expand on these results by evaluating outcomes by sex and mediation of those outcomes by anticoagulation. The

reasons for lower anticoagulation with DOACs, relative to warfarin, among women in the United States is still unclear, especially since there are data specifically supporting the advantages of DOACs versus warfarin in women.[31] The seminal DOAC trials enrolled 35% to 40% women and did not show any treatment heterogeneity in men versus women. Still, women might be perceived in some situations to be more frail and have lower body mass and, as such, may be prescribed lower doses of the same medications, sacrificing efficacy.[29]

Along with worse stroke outcomes, women were more likely to experience hospitalization after a new

diagnosis AF compared with men. Reasons for this are likely multifactorial, though prior data showing delays to referral for catheter ablation among women with AF[32] may be a marker of the overall delays to all forms of appropriate treatment for AF among women.[33] Worse outcomes coupled with the lower oral antico-agulation found in our study suggest that the high risk among women is not mirrored by appropriate clinical responses to mitigate this increased risk.

However, we also found that women were less likely to suffer ICH, in contrast to their higher bleeding risk when receiving other cardiovascular treatments.[34] While a number of risk factors for ICH have been es-tablished, such as hypertension[35] and older age,[36] our data actually showed a lower prevalence of many of these risk factors among women compared with men. The implication is that ICH without OAC is less com-mon in women, compared with men, at least among those with AF. The mediation of these offsetting risks (ischemic stroke, hospitalization versus ICH) by OAC in women suggests a nuanced influence of anticoagula-tion for both benefit and harm among women.

There important limitations to this study. Our study focuses on receipt of OAC drugs but does not ascertain actual pill consumption or adherence. While we could not exclude patients with all possible contraindications to anticoagulation, we did perform a subanalysis of patients categorized as "anticoag-ulation eligible." We also were unable to capture to what degree differences in anticoagulation may be attributable to differences in patient preferences by sex. Given that the CHA_2DS_2-VASc score did not be-come formally incorporated into US guidelines until 2014, it is possible that our cohort through 2015 only started to capture the response to guideline changes in the form of increased oral anticoagulation among women. Furthermore, the recent American Heart Association/American College of Cardiology/Heart Rhythm Society focused update to the guidelines in 2019[7] downgraded the class of recommendation for oral anticoagulation among women with CHA_2DS_2-Vasc scores of 2 from I to IIb; however, our cohort would not capture these recent changes. Because we used *ICD-9* codes for outcomes, we are de-pendent on the reliability of these selected codes, although high-specificity algorithms were used for outcomes. Because of limitations of the data source, we were not able to evaluate all-cause mortality. Finally, while we performed extensive adjustment for comorbidities and other demographics, confounding from unadjusted covariates may persist.

CONCLUSIONS

In patients with newly diagnosed of AF, receipt of oral anticoagulation, including DOACs, is substantially lower among women. Women, compared with men, had a high risk of ischemic stroke and hospitalization, and oral anticoagulation partially mediated the ob-served risk difference. OAC use also partially mediated ICH, although the absolute risk was small and compa-rable with men.
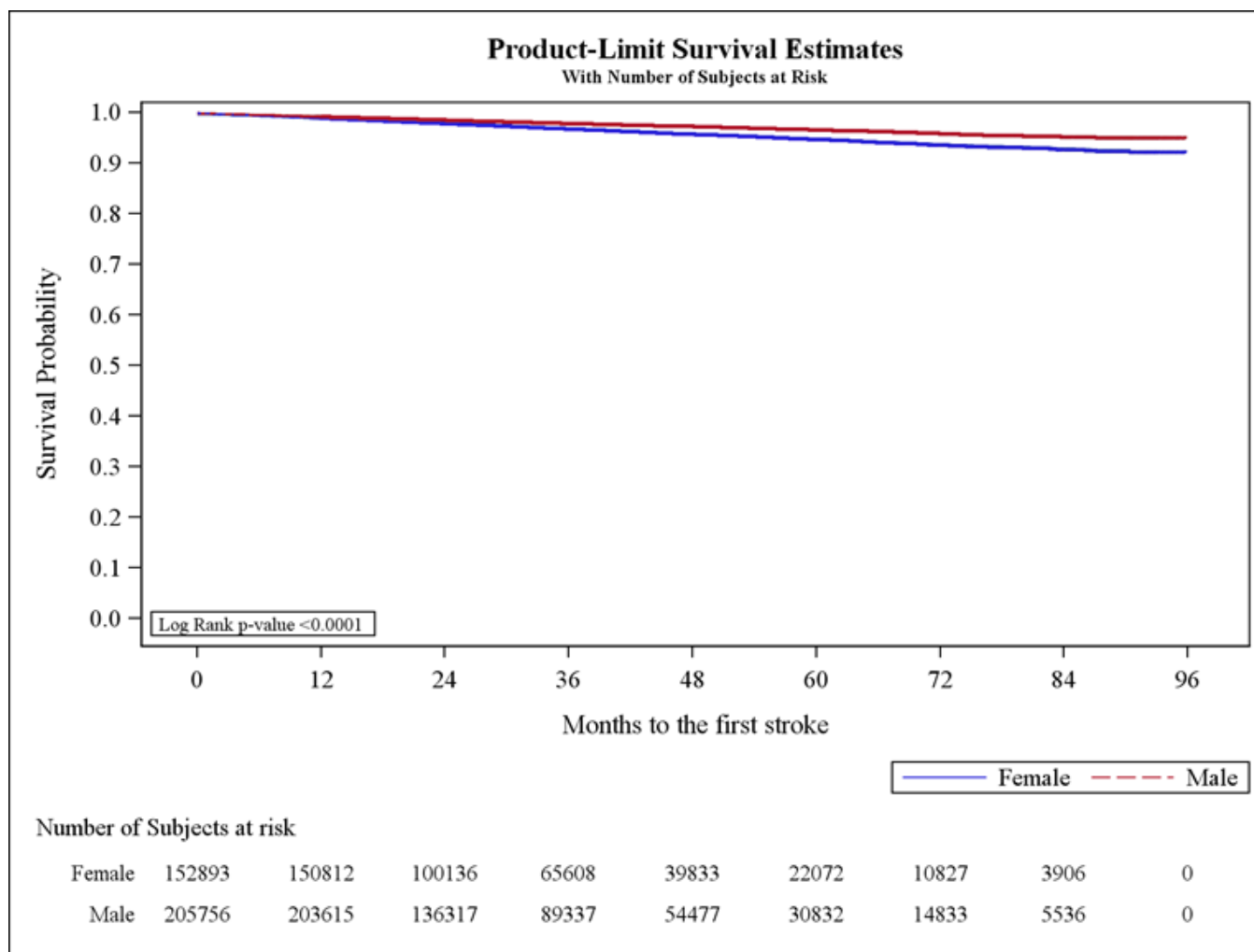
REFERENCES

1. Friberg J, Scharling H, Gadsboll N, Truelsen T, Jensen GB. 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.
2. 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.
3. 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.
4. Avgil Tsadok M, Jackevicius CA, Rahme E, Humphries KH, Behlouli H, Pilote L. Sex differences in stroke risk among older pa-tients with recently diagnosed atrial fibrillation. *JAMA*. 2012;307: 1952–1958.
5. Camm AJ, Lip GYH, De Caterina R, Savelieva I, Atar D, Hodnloser SH, Hindricks G, Kirchhof P; ESC Committee for Practice Guidelines (CPG), Bax JJ. 2012 focused update of the ESC Guidelines for the manage-ment of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contri-bution of the European Heart Rhythm Association. *Eur Heart J*. 2012; 33:2719–2747.
6. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, et al. 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.

7. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC, Ellinor PT, Ezekowitz MD, Field ME, Furie KL, et al. 2019 AHA/ACC/HRS focused update of the 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 Clinical Practice Guidelines and the Heart Rhythm Society. *Heart Rhythm*. 2019;16:e66–e93.

8. Reeves MJ, Fonarow GC, Zhao X, Smith EE, Schwamm LH. Quality of care in women with ischemic stroke in the GWTG program. *Stroke*. 2009;40:1127–1133.

9. Lapner ST, Cohen N, Kearon C. Influence of sex on risk of bleeding in anticoagulated patients: a systematic review and meta-analysis. *J Thromb Haemost*. 2014;12:595–605.

10. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361:1139–1151.

11. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365:981–992.

12. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365:883–891.

13. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;37:2893–2962.

14. Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, Carnethon MR, Dai S, De Simone G, Ford ES, et al. Heart disease and stroke statistics–2011 update: a report from the American Heart Association. *Circulation*. 2011;123:e18–e209.

15. Wolf PA, Benjamin EJ, Belanger AJ, Kannel WB, Levy D, D'Agostino RB. Secular trends in the prevalence of atrial fibrillation: the Framingham Study. *Am Heart J*. 1996;131:790–795.

16. Turakhia MP, Santangeli P, Winkelmayer WC, Xu X, Ullal AJ, Than CT, Schmitt S, Holmes TH, Frayne SM, Phibbs CS, Yang F. Increased mortality associated with digoxin in contemporary patients with atrial fibrillation: findings from the TREAT-AF study. *J Am Coll Cardiol*. 2014; 64:660–668.

17. Chang AY, Askari M, Fan J, Heidenreich PA, Michael Ho P, Mahaffey KW, Ullal AJ, Perino AC, Turakhia MP. Association of Healthcare Plan with atrial fibrillation prescription patterns. *Clin Cardiol*. 2018;41:1136–1143.

18. Ullal AJ, Kaiser DW, Fan J, Schmitt SK, Than CT, Winkelmayer WC, Heidenreich PA, Piccini JP, Perez MV, Wang PJ, et al. Safety and clinical outcomes of catheter ablation of atrial fibrillation in patients with chronic kidney disease. *J Cardiovasc Electrophysiol*. 2017;28:39–48.

19. Yong CM, Liu Y, Apruzzese P, Doros G, Cannon CP, Maddox TM, Gehi A, Hsu JC, Lubitz SA, Virani S, et al. Association of insurance type with receipt of oral anticoagulation in insured patients with atrial fibrillation: A report from the American College of Cardiology NCDR PINNACLE registry. *Am Heart J*. 2018;195:50–59.

20. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol*. 1986;51:1173–1182.

21. Perino AC, Fan J, Schmitt SK, Askari M, Kaiser DW, Deshmukh A, Heidenreich PA, Swan C, Narayan SM, Wang PJ, et al. Treating specialty and outcomes in newly diagnosed atrial fibrillation: from the TREAT-AF study. *J Am Coll Cardiol*. 2017;70:78–86.

22. 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.

23. Frich JC, Malterud K, Fugelli P. Women at risk of coronary heart disease experience barriers to diagnosis and treatment: a qualitative interview study. *Scand J Prim Health Care*. 2006;24:38–43.

24. Greenwood BN, Carnahan S, Huang L. Patient-physician gender concordance and increased mortality among female heart attack patients. *Proc Natl Acad Sci USA*. 2018;115:8569–8574.

25. Center for Workforce Studies. 2014 Physician Specialty Data Book. Association of American Medical Colleges. Available at: https://www.aamc.org/data-reports/workforce/interactive-data/active-physicians-sex-and-specialty-2017. Accessed April 30, 2020.

26. U.S. Department of Health and Human Services, Health Resources and Services Administration. *Women's Health USA 2011*. Rockville, MD: U.S. Department of Health and Human Services; 2011.

27. Lip GYH, Rushton-Smith SK, Goldhaber SZ, Fitzmaurice DA, Mantovani LG, Goto S, Haas S, Bassand JP, Camm AJ, Ambrosio G, et al. Does sex affect anticoagulant use for stroke prevention in nonvalvular atrial fibrillation? The prospective global anticoagulant registry in the FIELD-atrial fibrillation. *Circ Cardiovasc Qual Outcomes*. 2015;8:S12–S20.

28. Bhave PD, Lu X, Girotra S, Kamel H, Vaughan Sarrazin MS. Race- and sex-related differences in care for patients newly diagnosed with atrial fibrillation. *Heart Rhythm*. 2015;12:1406–1412.

29. Avgil Tsadok M, Jackevicius CA, Rahme E, Humphries KH, Pilote L. Sex differences in dabigatran use, safety, and effectiveness in a population-based cohort of patients with atrial fibrillation. *Circ Cardiovasc Qual Outcomes*. 2015;8:593–599.

30. Thompson LE, Maddox TM, Lei L, Grunwald GK, Bradley SM, Peterson PN, Masoudi FA, Turchin A, Song Y, Doros G, et al. Sex differences in the use of oral anticoagulants for atrial fibrillation. A report from the National Cardiovascular Data Registry (NCDR((R))) PINNACLE Registry. *J Am Heart Assoc*. 2017;6:e005801. DOI: 10.1161/JAHA.117.005801.

31. 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.

32. Patel D, Mohanty P, Di Biase L, Sanchez JE, Shaheen MH, Burkhardt JD, Bassouni M, Cummings J, Wang Y, Lewis WR, et al. Outcomes and complications of catheter ablation for atrial fibrillation in females. *Heart Rhythm*. 2010;7:167–172.

33. Moseley A, Doukky R, Williams KA, Jaffer AK, Volgman AS. Indirect comparison of novel oral anticoagulants in women with nonvalvular atrial fibrillation. *J Womens Health (Larchmt)*. 2017;26:214–221.

34. Mehta SK, Frutkin AD, Lindsey JB, House JA, Spertus JA, Rao SV, Ou FS, Roe MT, Peterson ED, Marso SP. Bleeding in patients undergoing percutaneous coronary intervention: the development of a clinical risk algorithm from the National Cardiovascular Data Registry. *Circ Cardiovasc Interv*. 2009;2:222–229.

35. Zia E, Hedblad B, Pessah-Rasmussen H, Berglund G, Janzon L, Engstrom G. Blood pressure in relation to the incidence of cerebral infarction and intracerebral hemorrhage. Hypertensive hemorrhage: debated nomenclature is still relevant. *Stroke*. 2007;38:2681–2685.

36. Flaherty ML, Kissela B, Woo D, Kleindorfer D, Alwell K, Sekar P, Moomaw CJ, Haverbusch M, Broderick JP. The increasing incidence of anticoagulant-associated intracerebral hemorrhage. *Neurology*. 2007;68:116–121.

SUPPLEMENTAL MATERIAL

Figure S1. Kaplan-Meier plot for ischemic stroke by sex.

Product-Limit Survival Estimates
With Number of Subjects at Risk

Log Rank p-value <0.0001

Months to the first stroke

Female ——— Male - - - -

Number of Subjects at risk

Female	152893	150812	100136	65608	39833	22072	10827	3906	0
Male	205756	203615	136317	89337	54477	30832	14833	5536	0

Women experience higher rates of ischemic stroke compared to men after a new AF diagnosis (p<0.0001).