

Sex Differences in Stroke Risk Among Older Patients With Recently Diagnosed Atrial Fibrillation

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ATRIAL FIBRILLATION (AF) is the most common cardiac arrhythmia, accounting for approximately one-third of hospitalizations for cardiac rhythm disturbances. It has been estimated that 2.2 million people in the United States and 4.5 million in the European Union have paroxysmal or persistent AF.¹

Patients with AF have a 5-fold increase in the risk of stroke compared with the general population²; therefore, antithrombotic agents are prescribed to reduce this risk.¹ Sex-based differences related to AF have been identified, the most concerning being that women with AF have an increased risk for cardiovascular events, including stroke.^{3,4} Previous studies have indicated that the annualized rate of stroke is 3% in women compared with 1.6% in men.⁵⁻⁹ This sex-based difference in patients with AF is concerning and not clearly understood. Underutilization of oral anticoagulation treatment among women has been suggested to be a contributing factor.¹⁰⁻¹² To date, it is not clear if the higher risk of stroke in women is a consequence of insufficient warfarin treatment.

Context Stroke is a serious complication associated with atrial fibrillation (AF). Women with AF are at higher risk of stroke compared with men. Reasons for this higher stroke risk in women remain unclear, although some studies suggest that undertreatment with warfarin may be a cause.

Objective To compare utilization patterns of warfarin and the risk of subsequent stroke between older men and women with AF at the population level.

Design, Setting, and Patients Population-based cohort study of patients 65 years or older admitted to the hospital with recently diagnosed AF in the province of Quebec, Canada, 1998-2007, using administrative data with linkage between hospital discharge, physicians, and prescription drug claims databases.

Main Outcome Measures Risk of stroke.

Results The cohort comprised 39 398 men (47.2%) and 44 115 women (52.8%). At admission, women were older and had a higher CHADS₂ (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischemic attack) score than men (1.99 [SD, 1.10] vs 1.74 [SD, 1.13], $P < .001$). At 30 days postdischarge, 58.2% of men and 60.6% of women had filled a warfarin prescription. In adjusted analysis, women appeared to fill more warfarin prescriptions compared with men (odds ratio, 1.07 [95% CI, 1.04-1.11]; $P < .001$). Adherence to warfarin treatment was good in both sexes. Crude stroke incidence was 2.02 per 100 person-years (95% CI, 1.95-2.10) in women vs 1.61 per 100 person-years (95% CI, 1.54-1.69) in men ($P < .001$). The sex difference was mainly driven by the population of patients 75 years or older. In multivariable Cox regression analysis, women had a higher risk of stroke than men (adjusted hazard ratio, 1.14 [95% CI, 1.07-1.22]; $P < .001$), even after adjusting for baseline comorbid conditions, individual components of the CHADS₂ score, and warfarin treatment.

Conclusion Among older patients admitted with recently diagnosed AF, the risk of stroke was greater in women than in men, regardless of warfarin use.

JAMA. 2012;307(18):1952-1958

www.jama.com

The American Heart Association 2011 guidelines for the prevention of cardiovascular disease in women¹³ em-

phasizes the need for reporting of sex-specific analyses for both efficacy and adverse effects of preventive interven-

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tions to inform the development of future sex-specific guidelines.

Using a unique population-based cohort of elderly patients with AF, we compared utilization patterns of warfarin and subsequent stroke incidence between men and women.

METHODS

Study Design

We conducted a retrospective cohort study of patients with AF, using administrative data with linkages between prescription drug claims, physician claims, and hospital discharge databases. The study received institutional review board approval from the McGill University Faculty of Medicine (study A05-M79-08B).

Study Population and Data Sources

Participants were Quebec residents 65 years or older, discharged alive from the hospital with a primary diagnosis of AF or a major comorbid diagnosis (secondary diagnosis) of AF (*International Classification of Diseases, Ninth Revision [ICD-9]/International Statistical Classification of Diseases, 10th Revision [ICD-10]* codes 427.3, 427.31, or 427.32/148). The information was gathered in Quebec between January 1, 1998, and March 31, 2007. To gather a cohort of patients with recently diagnosed AF, we included only patients who did not have a previous hospital admission or physician visit with either a primary or secondary diagnosis of AF within the prior year.

For cohort identification, the hospital discharge database (Maintenance et Exploitation des Données pour l'Étude de la Clientèle Hospitalière [Med-Echo]) was used. Patients' encrypted health insurance numbers were used to link the Med-Echo database to the provincial physician and prescription claims database (la Régie de l'assurance maladie du Québec [RAMQ]) containing information on all outpatient prescriptions for patients 65 years or older as well as all inpatient and outpatient diagnostic and therapeutic procedures and outpatient visits in Quebec.

To identify only nontransient AF, we excluded patients for whom AF was listed as a postadmission complication, who were likely to have perioperative AF (defined as having undergone coronary artery bypass graft surgery, pericardial surgery, or structural cardiac repair within 30 days prior to AF diagnosis), or who had hyperthyroidism or thyrotoxicosis within the year prior to the index admission.

Patients were excluded if they were 105 years or older or did not have a valid health card number. We also excluded residents of chronic care facilities, because information on filled prescriptions is not available for these patients. For patients with more than 1 hospitalization for AF, the first date of discharge from such hospitalization was defined as the date of entry into the cohort (index date). We included patients only once if they were transferred between hospitals.

We used the Med-Echo database to obtain information on patient characteristics such as comorbid conditions (from the lists of secondary diagnoses in the hospital discharge records, using the specific ICD-9/ICD-10 codes) and length of hospital stay and to calculate the CHADS₂ (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischemic attack) score. A CHADS₂ score was calculated for each patient by assigning 1 point each for age 75 years or older, hypertension, diabetes mellitus, and heart failure and 2 points for previous stroke or transient ischemic attack (TIA), with a possible total score of 0 to 6 points.¹⁴ The components of the CHADS₂ score were defined using diagnoses coded within 1 year prior to the index admission with AF, including the index admission.

Our primary outcome was stroke at any point during follow-up (after index admission). Stroke was defined as cerebral thrombosis, embolism, or artery occlusion, including TIA and retinal infarct (ICD-9 codes 434, 435, 436, and 362.3 or ICD-10 codes I63, I64, G45 [excluding G45.4], and H34.1). Intracerebral hemorrhages were not in-

cluded as a primary outcome but were reported separately (ICD-9/ICD-10 codes 431 and 432/I61). The Med-Echo database was used to obtain information on admissions to hospital with the diagnosis of stroke (until March 31, 2007). Survival data were assessed using data from both Med-Echo and RAMQ. By combining these databases, we were able to obtain both in-hospital and out-of-hospital survival data. Survival data were available until December 31, 2007.

We used the RAMQ database to obtain information on medication prescriptions filled after discharge from index hospital admission. The province of Quebec, Canada, provides universal access to health care and prescription drugs for persons 65 years or older.

Adherence to warfarin treatment was assessed by the medication possession ratio (MPR), using a fixed time frame of 1 year.¹⁵ The MPR is defined as the number of days of medications supplied divided by 365 days. To avoid immortal time bias, the MPR analysis was restricted to patients who survived the first year after discharge.

Statistical Analysis

Descriptive statistics were used to compare demographic characteristics, comorbid conditions, and pattern of warfarin usage between men and women. Continuous variables are presented as mean (SD) or median and interquartile range as appropriate and were compared using the *t* test or Mann-Whitney *U* test. Dichotomous variables are presented as percentages and were compared by χ^2 test. Incidence rates of stroke and mortality were calculated as the number of events per 100 person-years of follow-up and were reported in women and men separately.

To identify independent determinants of stroke, multivariate analyses with Cox proportional hazards models were performed. Follow-up for each patient was terminated at the first diagnosis of stroke, at death, or at the end of study period. Logistic regression was used to determine adjusted odds ratios of warfarin prescription refill within 30 days

postdischarge. All models were adjusted for female sex, age, length of index hospitalization, type of AF diagnosis (primary vs secondary), CHADS₂ score components (age was entered as a continuous variable), other comorbid conditions, and use of rate-control and rhythm-control drugs. In the multivariate analysis for the risk of stroke and mortality, we also adjusted for warfarin prescription filled within 30 days postdischarge from index admission. Results are expressed as hazard ratios or odds ratios with 95% confidence intervals.

A first sensitivity analysis was conducted by repeating the models in the subgroup of patients without a history of stroke; a second sensitivity analysis was conducted in more defined age groups (5-year intervals). A third sensitivity analysis was conducted only in patients who filled prescriptions for warfarin (within 30 days postdischarge from index admission), and a fourth sensitivity analysis was conducted in patients 80 years or younger, because the mortality rate in this age group is relatively lower.

All statistical analyses were performed using the SAS version 9.2. All statistical tests were 2-sided; $P < .05$ was considered statistically significant.

RESULTS

Baseline Characteristics

The cohort comprised 39 398 men (47.2%) and 44 115 women (52.8%). Women were older and had fewer comorbid conditions, with the exception of a history of valvular heart disease (TABLE 1). Congestive heart failure and diabetes were less frequent among women than among men, whereas hypertension and a history of stroke were more prevalent in women. In addition, 74.2% of women were older than 75 years, compared with only 61.4% of men. Thus, stroke risk was higher in women than in men, as reflected in the higher mean CHADS₂ score (1.99 [SD, 1.10] vs 1.74 [SD, 1.13], $P < .001$).

Utilization Patterns of Warfarin

Warfarin prescription rates were slightly higher among women compared with men (60.6% in women vs 58.2% in men, $P < .001$), in age groups 75 years or older (58.9% vs 56.4%, $P < .001$) and in patients younger than 75 years (65.4% vs 61.1%, $P < .001$). In multivariate analysis, women tended to have more prescriptions filled for warfarin within 30 days postdischarge, compared with men (odds ratio, 1.07; 95% CI, 1.04-1.11). The proportions of warfarin prescriptions filled were slightly increased to 68% in women as well as men when prescription rates were assessed within 1 year after discharge. Warfarin doses initially prescribed were higher among men compared with women. Adherence to warfarin was good in both sexes, represented by a mean MPR of 80% or greater (Table 1).

Stroke Outcome

Crude stroke rates were significantly higher in women compared with men (5.8% [95% CI, 5.6%-6.1%] vs 4.3% [95% CI, 4.1%-4.5%], $P < .001$). Most of the events were classified as cerebral thrombosis, embolism, or artery occlusion (5.2% in women vs 4.5% in

Table 1. Baseline Characteristics and Patterns of Warfarin Use by Sex

Characteristic	No. (%)	
	Women (n = 44 115)	Men (n = 39 398)
Patients diagnosed with AF		
AF as a main diagnosis	11 887 (26.9)	8506 (21.6)
AF as a secondary diagnosis	31 811 (72.1)	30 448 (77.3)
Patient characteristics		
Age at the index AF admission, median (IQR), y ^a	80.2 (74.8-85.4)	77.2 (72.2-82.4)
Length of hospitalization, median (IQR), d ^b	8 (4-6)	7 (4-4)
Comorbid conditions ^c		
Coronary artery disease	18 029 (40.9)	19 960 (50.7)
Hyperlipidemia	9210 (20.9)	9784 (24.8)
Chronic kidney disease	6024 (13.7)	7489 (19.0)
Acute myocardial infarction	5826 (13.2)	8192 (20.8)
Valvular heart disease	9519 (21.6)	6576 (16.7)
Bleeding event	2159 (4.9)	3107 (7.9)
Specific components of CHADS ₂ score ^c		
Congestive heart failure	12 283 (27.8)	11 403 (28.9)
Hypertension	28 197 (63.9)	20 205 (51.3)
Age \geq 75 y	32 740 (74.2)	24 205 (61.4)
Diabetes	9766 (22.1)	9702 (24.6)
History of stroke	3511 (8.0)	2733 (6.9)
CHADS ₂ score, mean (SD)	1.99 (1.10)	1.74 (1.13)
Warfarin first filled prescription		
Within 30 d postdischarge	26 715 (60.6)	22 939 (58.2)
Age <75 y	7441/11 375 (65.4)	9283/15 193 (61.1)
Age \geq 75 y	19 274/32 740 (58.9)	13 656/24 205 (56.4)
Within 90 d postdischarge	28 974/44 115 (65.7)	25 500/39 398 (64.7)
Within 365 d postdischarge	29 156/42 810 (68.1)	25 792/38 188 (67.5)
Warfarin initial prescription dose, median (IQR), mg	3.3 (2.0-5.0)	4.0 (2.9-6.0)
Adherence to warfarin ^d		
MPR for warfarin, 1 y postdischarge, mean (SD), %	81 (26)	80 (26)
MPR \geq 80% 1 y postdischarge	17 381 (67.2)	14 129 (63.8)

Abbreviations: AF, atrial fibrillation; CHADS₂, congestive heart failure, hypertension, age \geq 75 years, diabetes mellitus, prior stroke or transient ischemic attack; IQR, interquartile range; MPR, medication possession ratio.

^aFirst admission at which AF was coded as principal or secondary diagnosis.

^bLength of stay during hospitalization, including transfers to a different hospital.

^cWithin 1 year prior to AF admission.

^dMPR was assessed only among warfarin users (22 154 men, 25 865 women).

men, $P < .001$), whereas the rates of TIA or retinal infarction were lower (TIA: 2.6% in women vs 2.3% in men, $P = .003$; retinal infarction: 0.2% in women vs 0.2% in men, $P = .57$). The overall incidence of stroke was 2.02 (95% CI, 1.95-2.10) per 100 person-years in women vs 1.61 (95% CI, 1.54-1.69) per 100 person-years in men ($P < .001$) (TABLE 2).

Excluding TIA and retinal infarction from our stroke definition did not alter the results. The difference between sexes was mainly driven by the rates in the older (≥ 75 years) patients (2.38 per 100 person-years [95% CI, 2.28-2.49] in women vs 1.95 [95% CI, 1.84-2.07] in men, $P < .001$). Furthermore, older women had significantly higher rates of stroke than older men, regardless of warfarin use (FIGURE), and women had higher rates of stroke compared with men, regardless of adherence level (Table 2).

Stroke incidence rates were higher as CHADS₂ score increased. Differences in stroke incidence between men and

women were observed throughout the range of scores; however, differences reached statistical and clinical significance only in scores of 2 and 3 (Table 2).

In multivariable Cox regression analysis, women had a higher risk of stroke than men (hazard ratio [HR], 1.14 [95% CI, 1.07-1.22]) (TABLE 3), even after adjusting for baseline comorbid conditions, individual components of the CHADS₂ score, and warfarin treatment.

We also studied the distribution of intracerebral hemorrhages among men and women. We found no difference in the frequency of hemorrhage (postdischarge) between sexes: there were 558 (1.42%) cases of hemorrhage in men vs 587 (1.33%) in women ($P = .29$). Most of the intracerebral hemorrhage events occurred while patients were receiving warfarin.

Sensitivity Analyses

A history of stroke was the strongest independent risk factor for stroke

(Table 3). Given that stroke history is the most powerful risk factor for stroke, we attempted to understand the influence of this risk factor by repeating the multivariate analysis in a subgroup of patients without a history of stroke. In this analysis, women still had a higher risk of future stroke compared with men (HR, 1.17 [95% CI, 1.09-1.23]).

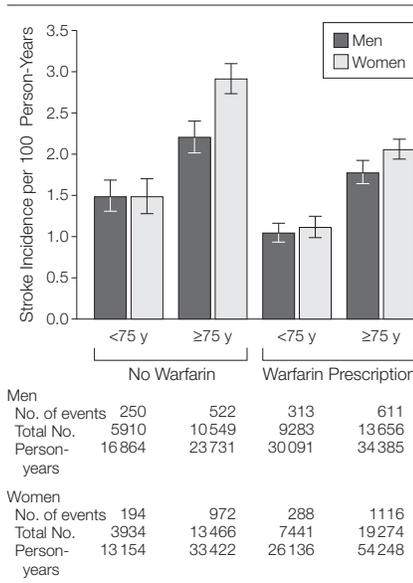
To further understand the possible modifying effect of age on the association between sex and the risk for stroke, we calculated the incidence of stroke (per 100 person-years) in more defined age categories, with intervals of 5 years (Table 2). We found that stroke incidence increased with age in both sexes and that women had higher incidence rates of stroke compared with men after age 75 years. We also repeated the Cox regression model in the different categories of the age groups (with intervals of 5 years) and found that after age 75 years, women had a statistically significant higher adjusted risk of stroke compared with men (HR,

Table 2. Number of Stroke Cases and Incidence Following Index Atrial Fibrillation Admission, by Sex

	Women (n = 44 115)		Men (n = 39 398)		P Value
	No.	Incidence per 100 Person-Years (95% CI)	No.	Incidence per 100 Person-Years (95% CI)	
Stroke events	2570	2.02 (1.95-2.10)	1696	1.61 (1.54-1.69)	<.001
Age group, y					
65-69	155	1.05 (0.89-1.23)	236	1.17 (1.03-1.33)	.34
70-74	327	1.33 (1.19-1.48)	327	1.22 (1.09-1.36)	.29
75-79	610	1.90 (1.75-2.05)	445	1.63 (1.48-1.79)	.02
80-84	672	2.26 (2.10-2.44)	385	1.99 (1.80-2.20)	.05
85-89	512	2.82 (2.58-3.07)	230	2.58 (2.26-2.93)	.28
90-94	246	3.81 (3.35-4.32)	62	2.72 (2.09-3.49)	.02
>95	48	4.02 (2.97-5.33)	11	3.56 (1.78-6.37)	.86
<75 y	482	1.23 (1.12-1.34)	563	1.20 (1.10-1.30)	.11
≥ 75 y	2088	2.38 (2.28-2.49)	1133	1.95 (1.84-2.07)	<.001
Warfarin adherence					
High (MPR $\geq 80\%$)	900	1.65 (1.54-1.76)	571	1.39 (1.28-1.51)	.03
Low (MPR <50%)	256	2.20 (1.94-2.49)	190	1.78 (1.54-2.05)	.001
CHADS ₂ score (No. of stroke events)					
0	114	1.03 (0.85-1.24)	130	0.86 (0.72-1.02)	.18
1	522	1.48 (1.36-1.61)	478	1.35 (1.23-1.47)	.14
2	964	2.05 (1.92-2.18)	546	1.67 (1.53-1.81)	<.001
3	583	2.48 (2.28-2.69)	313	2.01 (1.80-2.25)	.003
4	305	3.69 (3.29-4.13)	173	3.35 (2.87-3.89)	.32
5	75	4.91 (3.87-6.16)	45	4.88 (3.56-6.53)	>.99
6	7	2.29 (0.92-4.72)	11	8.05 (4.02-14.4)	.02

Abbreviations: CHADS₂, congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischemic attack; MPR, medication possession ratio.

Figure. Incidence of Stroke in Patients With and Without Prescriptions Filled for Warfarin in the First 30 Days Postdischarge, Stratified by Age Group and Sex



P = .96 and *P* < .001 for comparison of patients younger than 75 years and 75 years or older, respectively, in the group not receiving warfarin; *P* = .48 and *P* = .003 for comparison of patients younger than 75 years and 75 years or older, respectively, in the group receiving warfarin. Error bars indicate 95% confidence intervals.

1.18 [95% CI, 1.04-1.33] for the group aged 75-79 years; HR, 1.21 [95% CI, 1.06-1.37] for the group aged 80-84 years).

To test for a possible modification effect of age on the association between sex and stroke, we designed a multivariate model in which the age was expressed as a dichotomous variable (<75 and ≥75 years), and an interaction term was constructed accordingly. In this model, the interaction term was statistically significant (*P* = .02). These results illustrate that older women are a specific population at increased risk for stroke among patients with AF.

Considering the protective effect of warfarin, we also repeated our multivariate analysis only in the subgroup of patients who filled a warfarin prescription within 30 days postdischarge from AF index hospitalization. Even within this subgroup of patients, women continued to have a significantly higher risk for stroke compared with men (HR, 1.11 [95% CI, 1.02-1.21]).

Unadjusted mortality rates were higher among men compared with women (16.40 [95% CI, 16.17-16.62] vs 13.74 [95% CI, 13.55-13.93] per 100 person-years, *P* < .001), and this difference persisted irrespective of age. Because mortality rates were higher among men than women, it is possible that men did not live long enough to experience a stroke event. We repeated our analysis, focusing only on the population of patients aged 80 years or younger, as the mortality in this age group is lower, and found that female sex was still associated with a higher risk of stroke than male sex (HR, 1.10 [95% CI, 1.01-1.20]).

To limit the effect of aging on stroke outcome, we constructed 2 additional Cox regression models in which we restricted the follow-up time frame for a stroke event to 1 and 2 years. In these analyses, the risk for stroke still remained significantly higher in women compared with men (HR for 1 year, 1.25 [95% CI, 1.23-1.38]; HR for 2 years, 1.26 [95% CI, 1.16-1.37]), even after adjusting for age, warfarin use, and comorbid conditions.

Table 3. Multivariable Cox Regression Models for Risk of Stroke Among Patients With Atrial Fibrillation

	HR (95% CI) ^{a,b}	Stroke Events, No./Total	
		Patients With the Specific Condition	Patients Without the Specific Condition
Female, sex	1.14 (1.07-1.22)	2570/44 115	1696/39 398
Age, per 1 y ^c	1.04 (1.03-1.04)	NA	NA
≥75 y	NA	3221/56 945	1045/26 568
Comorbid conditions			
Coronary artery disease	1.05 (0.98-1.13)	1921/37 989	2345/45 524
Chronic kidney disease	1.09 (1.00-1.20)	609/13 513	3657/70 000
Acute myocardial infarction	0.97 (0.89-1.07)	665/14 018	3601/69 495
Valvular heart disease	0.97 (0.89-1.05)	781/16 095	3485/67 418
Bleeding event	1.10 (0.97-1.24)	276/5266	3990/78 247
Specific components of CHADS ₂ score			
Congestive heart failure	1.01 (0.94-1.09)	1091/23 686	3175/59 827
Hypertension	1.08 (1.01-1.15)	2595/48 402	1671/35 111
Diabetes	1.20 (1.11-1.29)	1025/19 468	3241/64 045
History of stroke	2.44 (2.24-2.65)	707/6244	3559/77 269
Warfarin treatment ^d	0.75 (0.71-0.80)	2328/49 654	1938/33 859

Abbreviations: CHADS₂, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack; HR, hazard ratio; NA, not applicable.

^aModels were also adjusted for other comorbid conditions (hyperlipidemia), length of hospitalization, type of diagnosis (primary or secondary), and use of rate-control and rhythm-control drugs.

^b*n* = 83 513 (*n* = 4266 stroke events).

^cAge considered a continuous variable.

^dPrescription claim within 30 days following index admission as categorical variable.

COMMENT

Results from this study indicate that women, especially those 75 years or older, have a higher risk of stroke than men, regardless of their risk profile and use of warfarin. These results suggest that current anticoagulant therapy to prevent stroke might not be sufficient for older women, and new strategies are needed to further reduce stroke risk in women with AF.

Higher stroke rates in women with AF have been demonstrated in the Framingham Heart Study,¹⁶ the Stroke Prevention in Atrial Fibrillation (SPAF) trials,⁵ the Anticoagulation and Risk factors in Atrial Fibrillation (ATRIA) study,⁶ and the Stroke Prevention Using an Oral Thrombin Inhibitor in Patients With AF (SPORTIF) trials⁸ as well as in a cohort study of patients with AF receiving chronic warfarin treatment.⁹ In these studies, women had a 40% to 70% increased risk for stroke compared with men, which occurred re-

ardless of whether patients received anticoagulants but which was mainly attributed to women not receiving warfarin. The results of our current population-based study are consistent with earlier research and confirm a 14% higher risk for stroke in women, irrespective of warfarin therapy.

The evidence regarding discrepancies in warfarin treatment between men and women with AF is inconsistent. A few studies have concluded that women were less likely to receive warfarin than men,^{10,17,18} whereas other studies have concluded that the quality of anticoagulation and prescription of anticoagulants did not differ between sexes.^{7,9,19} In our current study, we found that women had a higher chance of filling a prescription for warfarin; therefore, it appears unlikely that differences in warfarin prescription between the sexes are the main explanation for the higher stroke rates in women. We also noticed that the initial prescription dose of warfarin was higher in men than women. However, unlike dosages of other medications, warfarin dosage has no clinical meaning without the international normalized ratio, because therapeutic dose differs between patients, and a high dose in one patient may be equal to a low dose in another. Therefore, we cannot claim that women were treated less aggressively with warfarin compared with men.

Given that women are as likely as men to fill prescriptions for warfarin, we further studied if adherence to warfarin prescription differed between sexes. We found that in general, adherence to anticoagulation therapy was relatively high and similar in both sexes, which is consistent with findings from a previous study.²⁰ Therefore, although important, adherence to warfarin treatment is not the key reason for the higher risk of stroke in women compared with men.

Except for female sex, the major risk factors associated with stroke were previous stroke and advanced age. Considering these risk factors as dominant predictors for stroke, we

demonstrated in additional sensitivity analyses that female sex is an independent risk factor for stroke among patients without a history of stroke; therefore, previous stroke was not the main explanation for the sex difference. Additionally, keeping in mind that the older population has a higher risk of stroke, we evaluated the risk for stroke in different age groups within our population and found that the specific population at increased risk for stroke is older women.

Several risk stratification schemes have been developed to help clinicians gauge stroke risk in individual patients with AF and to guide the use of anticoagulation therapy. To date, female sex is incorporated as a risk factor in the Framingham stroke risk score¹⁶ and classified into “less validated or weaker risk factors” in the American College of Cardiology/American Heart Association/European Society of Cardiology guidelines¹ but is not incorporated in the frequently used CHADS₂ score.¹⁴ In an attempt to improve risk stratification of CHADS₂, the refined CHA₂DS₂-VASc (congestive heart failure, hypertension, age 65-74 years, age \geq 75 years, diabetes mellitus, prior stroke or transient ischemic attack, female sex, vascular disease) score was introduced, including female sex as a risk factor for stroke.²¹ However, the CHA₂DS₂-VASc score was not meant to replace CHADS₂ but to complement it for evaluation of patients with CHADS₂ scores less than 2.²² As indicated by our study results, women have higher rates of stroke in the intermediate range of CHADS₂ scores; therefore, it is possible that CHADS₂ does not address a potential sex gap in the population of patients with intermediate risk and that there is a need to incorporate sex in risk scores to evaluate the need for warfarin therapy in all patients with AF. We believe that future sex-based assessment of and recommendations for stroke risk will help close the gap between sexes. Adequate risk scores incorporating sex will require further evaluation.

Older patients (\geq 75 years) are the most vulnerable population, in whom rates of AF are the highest and the risk of stroke is the greatest. In line with the results of a previous study,²³ the rates of major stroke in the older population of our study were higher in women compared with men. With the longer life expectancy of women and the direct relationship between stroke and advanced age, older women will bear the major burden of disease. Thus, women older than 75 years represent the most important target population for stroke prevention in patients with AF, and the effectiveness of novel anticoagulants in this population in real-world practice will need to be closely monitored. Lack of information from clinical trials on these agents in older women and the current high cost of novel anticoagulants will not enable them to entirely displace warfarin, and it is likely that warfarin will continue to be used worldwide in patients with AF. Therefore, the results from our current study on warfarin treatment in real-world practice has essential value, because they emphasize patients' sex as a major risk factor for stroke within the currently accessible and existing treatment protocols.

It is not yet known why women with AF are more susceptible to stroke. Further prospective studies are needed to evaluate this increased risk in women. The increased risk may be attributable to physiology (such as uncontrolled hypertension), vascular biology, genetic factors, hormonal or thromboembolic factors, or psychosocial factors that differ between men and women. We were not able to identify these factors with our database. Further studies should focus on these possible explanations for the sex differences in stroke rates.

Some limitations of the study should be noted. This study was designed as a retrospective study and as such has inherent limitations and biases. For example, the use of administrative datasets to estimate stroke, CHADS₂ score, and comorbid conditions may be subject to misclassification biases, because it is

possible that clinicians diagnose men and women differently. We also were unable to identify important clinical factors such as international normalized ratio levels, type of AF, or severity of stroke within our database. Another limitation is the restriction of our study to patients 65 years or older, owing to the availability of data on prescription claims. However, given that AF and stroke mainly affect older patients, the age restriction is less of a concern. Nevertheless, the size of our study population and the unique design of a population-based study are strong advantages of this study that advance the current knowledge on stroke risk in patients with AF.

Although epidemiologic studies have investigated sex differences in

stroke occurrence, little is known about warfarin effectiveness between men and women in the real-world clinical setting. Our results suggest that elderly women with AF may need to be targeted for more effective stroke prevention therapy. Clinicians should be aware of the elevated stroke risk in older women with AF, and new strategies should be applied to effectively prevent stroke equally in men and women.

Author Contributions: Dr Pilote had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Avgil Tsadok, Jackevicius, Humphries, Pilote. *Acquisition of data:* Avgil Tsadok, Behloul, Pilote. *Analysis and interpretation of data:* Avgil Tsadok, Jackevicius, Rahme, Pilote. *Drafting of the manuscript:* Avgil Tsadok, Rahme, Pilote.

Critical revision of the manuscript for important intellectual content: Avgil Tsadok, Jackevicius, Humphries, Behloul, Pilote.

Statistical analysis: Avgil Tsadok, Rahme, Behloul.

Obtained funding: Jackevicius, Pilote.

Administrative, technical, or material support: Avgil Tsadok.

Study supervision: Jackevicius, Pilote.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Avgil Tsadok reported receiving a fellowship award from the Canadian Institutes of Health Research (CIHR) and receiving a travel award from the CIHR to present the study results at a conference (American Heart Association 2011 Scientific Sessions). Dr Humphries reported receiving a new investigator award from the CIHR. Dr Pilote reported serving as a James McGill Chair at McGill University and receiving a national investigator award from the Fonds de recherche en santé du Québec.

Funding/Support: This study was supported by operating grant MOP-84304 from the CIHR.

Role of the Sponsor: The CIHR had no role in the design and conduct of the study; the collection, analysis, and interpretation of the data; or the preparation, review, or approval of the manuscript.

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