

# Stroke risk in women with atrial fibrillation

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## Abstract

**Background and aims** Female sex is associated with higher rates of stroke in atrial fibrillation (AF) after adjustment for other CHA<sub>2</sub>DS<sub>2</sub>-VASc factors. This study aimed to describe sex differences in age and cardiovascular care to examine their relationship with stroke hazard in AF.

**Methods** Population-based cohort study using administrative datasets of people aged ≥66 years diagnosed with AF in Ontario between 2007 and 2019. Cause-specific hazard regression was used to estimate the adjusted hazard ratio (HR) for stroke associated with female sex over a 2-year follow-up. Model 1 included CHA<sub>2</sub>DS<sub>2</sub>-VASc factors, with age modelled as 66–74 vs. ≥75 years. Model 2 treated age as a continuous variable and included an age–sex interaction term. Model 3 further accounted for multimorbidity and markers of cardiovascular care.

**Results** The cohort consisted of 354 254 individuals with AF (median age 78 years, 49.2% female). Females were more likely to be diagnosed in emergency departments and less likely to receive cardiologist assessments, statins, or LDL-C testing, with higher LDL-C levels among females than males. In Model 1, the adjusted HR for stroke associated with female sex was 1.27 (95% confidence interval 1.21–1.32). Model 2 revealed a significant age–sex interaction, such that female sex was only associated with increased stroke hazard at age >70 years. Adjusting for markers of cardiovascular care and multimorbidity further decreased the HR, so that female sex was not associated with increased stroke hazard at age ≤80 years.

**Conclusion** Older age and inequities in cardiovascular care may partly explain higher stroke rates in females with AF.

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## Structured Graphical Abstract

### Key Question

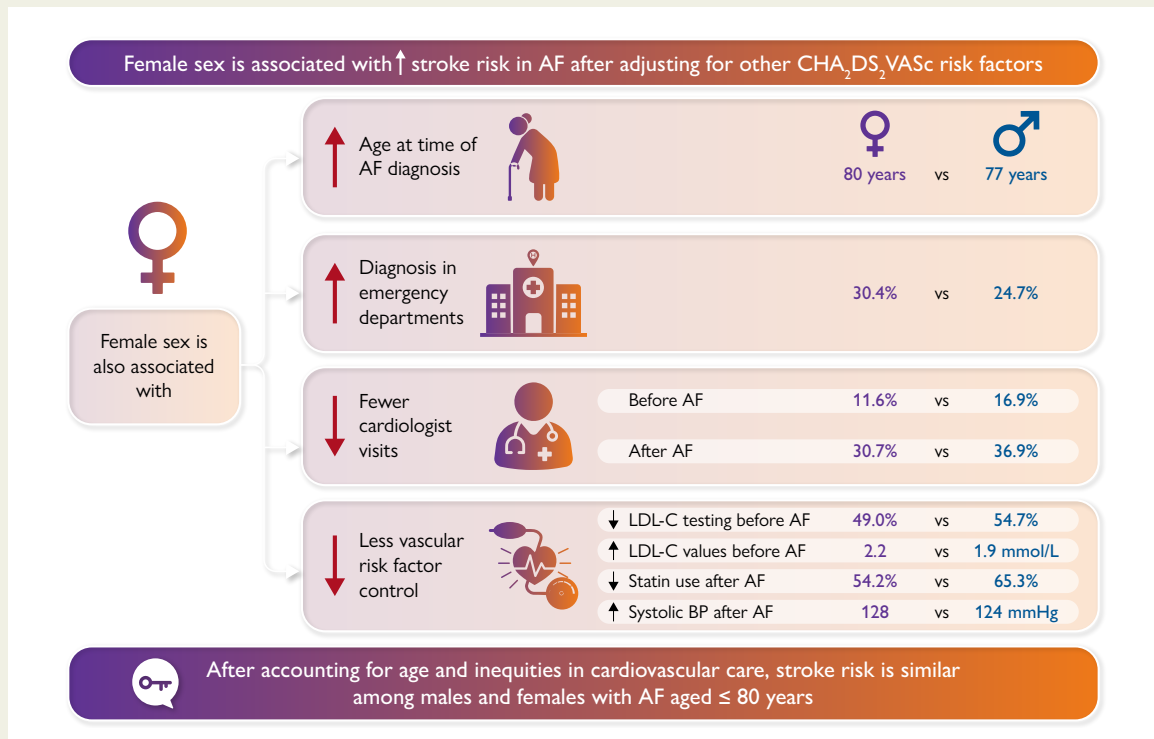
Is higher stroke risk associated with female sex in atrial fibrillation (AF) related to differences in age and cardiovascular preventive care?

### Key Finding

Female sex was associated with older age, more frequent AF diagnosis in emergency departments, fewer cardiologist visits, and less statin use. After accounting for these differences, stroke risk was similar among male and female AF patients aged  $\leq 80$  years.

### Take Home Message

After accounting for age and inequities in cardiovascular care, stroke risk is similar among males and females with AF aged  $\leq 80$  years.



Higher stroke risk among women with atrial fibrillation (AF) may be related to inequities in cardiovascular care, suggesting that reducing sex differences in cardiovascular care may attenuate the excess stroke risk in females with AF.

BP, blood pressure; CHA<sub>2</sub>DS<sub>2</sub>-VASc, congestive heart failure, hypertension, age  $\geq 75$  years (doubled), diabetes, stroke (doubled), vascular disease, age 66 to 74 years, and sex category (female); F, female; LDL-C, low density lipoprotein cholesterol; M, male.

**Keywords** Atrial Fibrillation • Stroke • Female sex

## Introduction

Female sex is assigned one point in the CHA<sub>2</sub>DS<sub>2</sub>-VASc score as it is associated with higher stroke risk in atrial fibrillation (AF).<sup>1</sup> Recent studies suggest that female sex is a risk modifier for AF-associated stroke rather than an independent risk factor in all-comers with AF.<sup>2,3</sup> We previously reported that female sex is not associated with increased stroke risk among people aged  $< 75$  years who do not have other CHA<sub>2</sub>DS<sub>2</sub>-VASc factors.<sup>4</sup> Conversely, females with AF have higher stroke risk than their male counterparts at older age or higher CHA<sub>2</sub>DS<sub>2</sub>-VASc scores.<sup>3</sup>

There are several potential explanations for a sex-based interaction between risk factors and stroke hazard. It may be that females are biologically

more predisposed towards stroke from risk factors (such as hypertension and diabetes), but there are alternative plausible explanations. Females tend to develop AF at an older age than males, and stroke rates rise in a graded manner with increasing age.<sup>4,5</sup> There may be greater sex-based inequities in risk factor control and appropriate anticoagulation among older patients,<sup>6</sup> so that the magnitude of a risk factor (e.g. blood pressure) may be higher in older females than males. Patients with AF remain at risk for non-embolic (i.e. atherosclerotic) strokes,<sup>7,8</sup> and the CHA<sub>2</sub>DS<sub>2</sub>-VASc score predicts stroke similarly in people with and without AF.<sup>9</sup> Aggressive management of vascular risk factors is associated with better outcomes after AF diagnosis.<sup>10,11</sup> Furthermore, females with AF may have lower socioeconomic status,<sup>12,13</sup> which is associated with less cardiovascular care and diagnosis of AF later in the disease course.

We present a population-based cohort study using administrative datasets to describe sex-based differences in cardiovascular treatment and the interaction between age and sex as it pertains to the hazard of stroke in people with newly recognized AF. Our hypothesis was that accounting for age as a continuous variable and adjusting for markers of cardiovascular care substantially attenuate the adjusted hazard ratio (HR) for stroke associated with female sex.

## Methods

### Data sources

Residents of Ontario (Canada's most populous province) receive universal health insurance through the Ontario Health Insurance Plan. Prescription medication coverage is provided for residents aged >65 years through the Ontario Drug benefit programme, with copayments of \$2–\$6.11 per prescription after a \$100 annual deductible.<sup>14</sup> Health services are administered via an insurance number unique to each person, allowing for linkage of administrative datasets for research purposes. The Canadian Institute for Health Information Discharge Abstract Database records data on hospitalized patients, whereas the National Ambulatory Care Reporting System collects data on emergency department (ED) visits. The Ontario Health Insurance Plan physician claims database records physician billing data, and the Registered Persons Database maintains vital statistics data (including dates of birth and death). The Ontario Laboratories Information System database contains information on laboratory test results, including LDL-C levels.<sup>15</sup> Canadian census data were used to determine neighbourhood-level socio-economic metrics.<sup>16</sup> The ICES Physician Database was used to obtain information on physician specialty. These datasets were linked using unique encoded identifiers and analysed at ICES (formerly called the Institute for Clinical Evaluative Sciences).<sup>17</sup> The methods underlying their use for cardiovascular research have been previously described.<sup>18</sup> The use of data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act,<sup>19</sup> which does not require review by a research ethics board.

### Cohort creation

We created a cohort of community-dwelling individuals aged  $\geq 66$  years who were diagnosed with AF or atrial flutter (henceforth referred to as AF) between April 2007 and March 2019. The AF was ascertained based on one record of AF in hospital or ED discharge records (ICD-10 I48), or four physician billing claims for ICD-9 code 427 in 365 days. This algorithm was validated to have a specificity of 99.1% [95% confidence interval (CI) 98.9%–99.3%] for AF.<sup>20</sup> The index date was that of first hospital, ED, or physician billing record indicative of AF. We excluded people with AF diagnoses in the prior 5 years to mostly capture people with newly recognized AF, since we were interested in studying cardiovascular care for people with AF at a comparable period in the disease trajectory. The exclusion criteria (detailed in [Figure 1](#)) also included valvular disease, as that subtype of AF has distinct clinical, therapeutic, and prognostic implications.

### Exposures

The key independent measure was female sex. Covariates of interest included other CHA<sub>2</sub>DS<sub>2</sub>-VASc risk factors: heart failure (HF), hypertension, age, diabetes, prior stroke/transient ischaemic attack (TIA), and vascular disease (defined as presence of ischaemic heart disease or peripheral vascular disease). We also studied several markers of cardiovascular care. Neighbourhood-level material deprivation is a marker of neighbourhood residents' inability to attain basic material needs,<sup>16</sup> which we previously reported to be associated with less cardiovascular care after AF diagnosis.<sup>12</sup> We identified location of first AF diagnosis, since being diagnosed in the ED or hospital may indicate less outpatient care and therefore less ability to have AF diagnosed and managed out-of-hospital. We also studied the following measures of cardiovascular care received in the year before AF

diagnosis: dispensation of statins, assessment by a cardiologist, receipt of echocardiography, testing for LDL-C, and achieved LDL-C level. Anticoagulation status after AF diagnosis was included as a time-varying covariate. To account for multimorbidity, we included estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation<sup>21</sup> and estimated frailty from prior hospitalization data using methods described by Gilbert et al.<sup>22</sup> The approaches used for determination of the key exposures are summarized in [Supplementary data online, Table S1](#).

### Outcome

The primary outcome was hospitalization with a most responsible diagnosis of ischaemic stroke [ICD-10 codes I63 (excluding I63.6), I64, and H341].<sup>23</sup> Follow-up was limited to 2 years after AF diagnosis, since people with AF frequently acquire additional stroke risk factors over time<sup>24</sup> and we expected a weaker relationship of factors measured before AF diagnosis with strokes beyond 2 years. We also studied cardiologist assessments, receipt of echocardiography, and dispensation of anticoagulation and statins as markers of cardiovascular care in the 2 years after AF diagnosis.

### Exploratory analyses

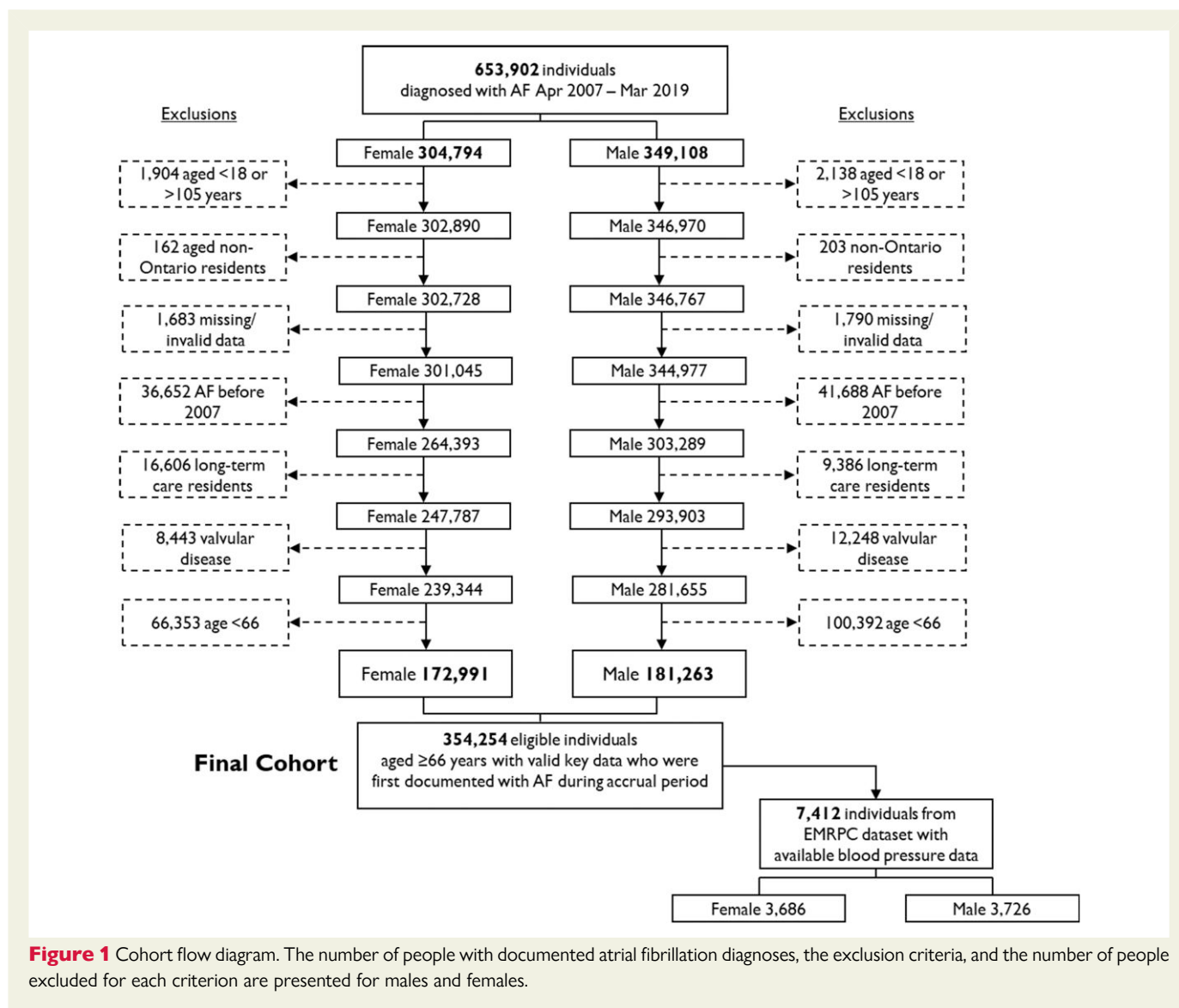
The Electronic Medical Records-Primary Care (EMRPC) database (previously known as EMRALD) contains clinical data from the electronic medical records of ~400 000 patients enrolled between April 2010 and March 2016 from ~400 primary care physician practices in Ontario.<sup>25</sup> Using individuals from our cohort who were also included in EMRPC, we compared differences by sex in blood pressure (BP) measurements. This subset was not used for multivariable regression analyses of stroke risk given its smaller sample size.

We also analysed appropriateness of direct-acting oral anticoagulant (DOAC) dosing among people in the full cohort who were unlikely to qualify for reduced DOAC dosing regardless of weight (which was unavailable for most participants). This was defined as people aged <80 years with creatinine <133  $\mu\text{mol/L}$  (1.5 mg/dL) and eGFR  $\geq 50$  mL/min (estimated using the CKD-EPI equation). We then studied the subset of participants in EMRPC with available weight data who had eGFR  $\geq 50$  mL/min and met <2 of the dose reduction criteria for apixaban (age  $\geq 80$  years, weight  $\leq 60$  kg, creatinine  $\geq 133$   $\mu\text{mol/L}$ ), as these people would be expected to qualify for the full dose of most DOACs.<sup>26</sup>

### Statistical methods

Missing values of LDL-C and eGFR were filled in using multiple imputation,<sup>27,28</sup> using previously described methods.<sup>29</sup> Multiple imputation allows one to avoid potential biases arising from a complete case analysis (i.e. using only subjects with no missing data). In this instance, subjects with missing LDL-C may have less healthcare contact than those with observed LDL-C. By imputing multiple values for each missing value, one can explicitly incorporate uncertainty in the value of the imputed data. The imputation model used all the variables listed in the exposure section as well as an indicator variable denoting the occurrence of ischaemic stroke and the cumulative hazard of ischaemic stroke at the time of stroke or censoring. We also utilized available values of LDL-C and eGFR for imputation of the alternate missing variable. The number of imputed samples was set to the percentage of missing observations (i.e. 48 complete samples were created).<sup>28</sup> Each statistical analysis was conducted in each imputed dataset, after which we pooled the regression coefficient estimates and their standard errors using Rubin's rules. For elements of past medical history, we considered that the person had the diagnosis if they fulfilled criteria for its determination within administrative datasets.

The cohort was stratified by sex for comparison of baseline characteristics, which were summarized using medians [with 25th–75th percentiles (Q1–Q3)] for continuous variables and counts (with percentages) for dichotomous variables. Given our large sample size, we focused on standardized differences<sup>30</sup> to determine the relevance of unadjusted sex-based



**Figure 1** Cohort flow diagram. The number of people with documented atrial fibrillation diagnoses, the exclusion criteria, and the number of people excluded for each criterion are presented for males and females.

differences in baseline characteristics, since they are less affected by sample size than the  $\chi^2$  or Wilcoxon rank sum tests. Standardized difference values  $\geq 0.1$  were considered to denote potentially meaningful differences.<sup>31</sup>

To contextualize sex differences in the crude rate of outcomes, we calculated the age-standardized event rate per 100 person-years with 95% CIs. Cause-specific hazard regression models were fit to study the association of female sex with the hazard of stroke over 2 years, with progressively comprehensive adjustment in three models. Death was treated as a competing risk. Model 1 only included the conventional CHA<sub>2</sub>DS<sub>2</sub>-VASc factors as predictors, with age as a binary variable (66–74 years, or  $\geq 75$  years). For subsequent analyses, age was handled as a continuous variable using restricted cubic splines with five knots placed at the 5%, 27.5%, 50%, 72.5%, and 95% percentiles.<sup>32</sup> To determine if the HR for female sex varied with age, we tested for statistical significance of an age–sex interaction term. The interaction term was significant, so Models 2 and 3 incorporated the CHA<sub>2</sub>DS<sub>2</sub>-VASc factors plus an age–sex interaction term. Model 3 further accounted for baseline multimorbidity and markers of cardiovascular care that are listed above (Exposures section). Model 3 also included anticoagulation as a four-level time-varying covariate (non-anticoagulated, warfarin-treated, low-dose DOAC, or full-dose DOAC). For Models 2 and 3, the HR for stroke associated with female sex is presented at yearly age intervals.

Statistical significance of regression analyses was defined as a two-tailed *P*-value  $< .05$ . All analyses were performed using SAS Enterprise Guide 7.1 (SAS Institute Inc., Cary, NC). Cells with  $< 6$  individuals were censored as per ICES' privacy policies.

## Results

### Baseline characteristics

We identified 354 254 community-dwelling individuals [172 991 (48.8%) females] aged  $\geq 66$  years diagnosed with AF between April 2007 and March 2019 who met study inclusion criteria (Figure 1). Their baseline characteristics are listed in Table 1. The overall median age was 78 (Q1–Q3 72–84) years. Females were older than males, with 25.9% of women aged  $> 85$  years compared to 16.1% of men (Figure 2). Females were more likely to be diagnosed in the ED than males (30.4% vs. 24.7%, standardized difference 0.13).

Males were more likely to have prior diabetes and vascular disease while females were more likely to have hypertension and lower

**Table 1** Baseline characteristics of male and female people with newly diagnosed atrial fibrillation

Variable	Females (n = 172 991)	Males (n = 181 263)	Standardized difference
Age, median (Q1–Q3)	<b>80 (74–86)</b>	<b>77 (72–83)</b>	<b>0.29</b>
Setting of first AF diagnosis			
In-hospital diagnosis, n (%)	47 042 (27.2)	55 289 (30.5)	0.07
Emergency department diagnosis, n (%)	<b>52 550 (30.4)</b>	<b>44 737 (24.7)</b>	<b>0.13</b>
Outpatient diagnosis, n (%)	73 399 (42.4)	81 237 (44.8)	0.05
Regional material deprivation quintile			
1, n (%)	30 330 (17.5)	35 248 (19.4)	0.05
2, n (%)	32 159 (18.6)	36 411 (20.1)	0.04
3, n (%)	33 607 (19.4)	36 435 (20.1)	0.02
4, n (%)	36 988 (21.4)	36 778 (20.3)	0.03
5, n (%)	38 577 (22.3)	34 978 (19.3)	0.07
Missing, n (%)	1330 (0.8)	1413 (0.8)	0.001
Congestive heart failure, n (%)	50 916 (29.4)	54 191 (29.9)	0.01
Hypertension, n (%)	<b>148 124 (85.6)</b>	<b>148 653 (82.0)</b>	<b>0.10</b>
Diabetes, n (%)	<b>52 566 (30.4)</b>	<b>67 952 (37.5)</b>	<b>0.15</b>
Prior stroke or TIA, n (%)	10 401 (6.0)	9698 (5.4)	0.03
Vascular disease, n (%)	<b>50 447 (29.2)</b>	<b>74 701 (41.2)</b>	<b>0.25</b>
Hospital frailty score, median (Q1–Q3)	1.6 (0–6)	1.5 (0–5)	0.03
Visited a cardiologist in prior year, n (%)	<b>20 032 (11.6)</b>	<b>30 669 (16.9)</b>	<b>0.15</b>
Echocardiogram in prior year, n (%)	85 080 (49.2)	96 704 (53.4)	0.08
LDL-C value (mmol/L), median (Q1–Q3)	<b>2.2 (1.6–2.9)</b>	<b>1.9 (1.4–2.6)</b>	<b>0.30</b>
eGFR, median (Q1–Q3)	<b>64 (48–79)</b>	<b>67 (51–81)</b>	<b>0.13</b>
No. of anti-hypertensive medicines			
0, n (%)	25 278 (14.6)	31 045 (17.1)	0.07
1, n (%)	35 154 (20.3)	38 215 (21.1)	0.02
2, n (%)	46 483 (26.9)	49 611 (27.4)	0.01
3, n (%)	44 594 (25.8)	43 194 (23.8)	0.05
4, n (%)	20 075 (11.6)	17 868 (9.9)	0.06
5, n (%)	1407 (0.8)	1330 (0.7)	0.01
Statins, n (%)	<b>83 608 (48.3)</b>	<b>107 946 (59.6)</b>	<b>0.23</b>
Any oral anticoagulant, n (%)	56 330 (32.6%)	61 541 (34.0%)	0.03
Full dose DOAC, n (%)	12 273 (7.1%)	15 026 (8.3%)	0.04
Reduced dose DOAC, n (%)	11 070 (6.4%)	8913 (4.9%)	0.06
Warfarin n (%)	34 503 (19.9%)	39 250 (21.7%)	0.04

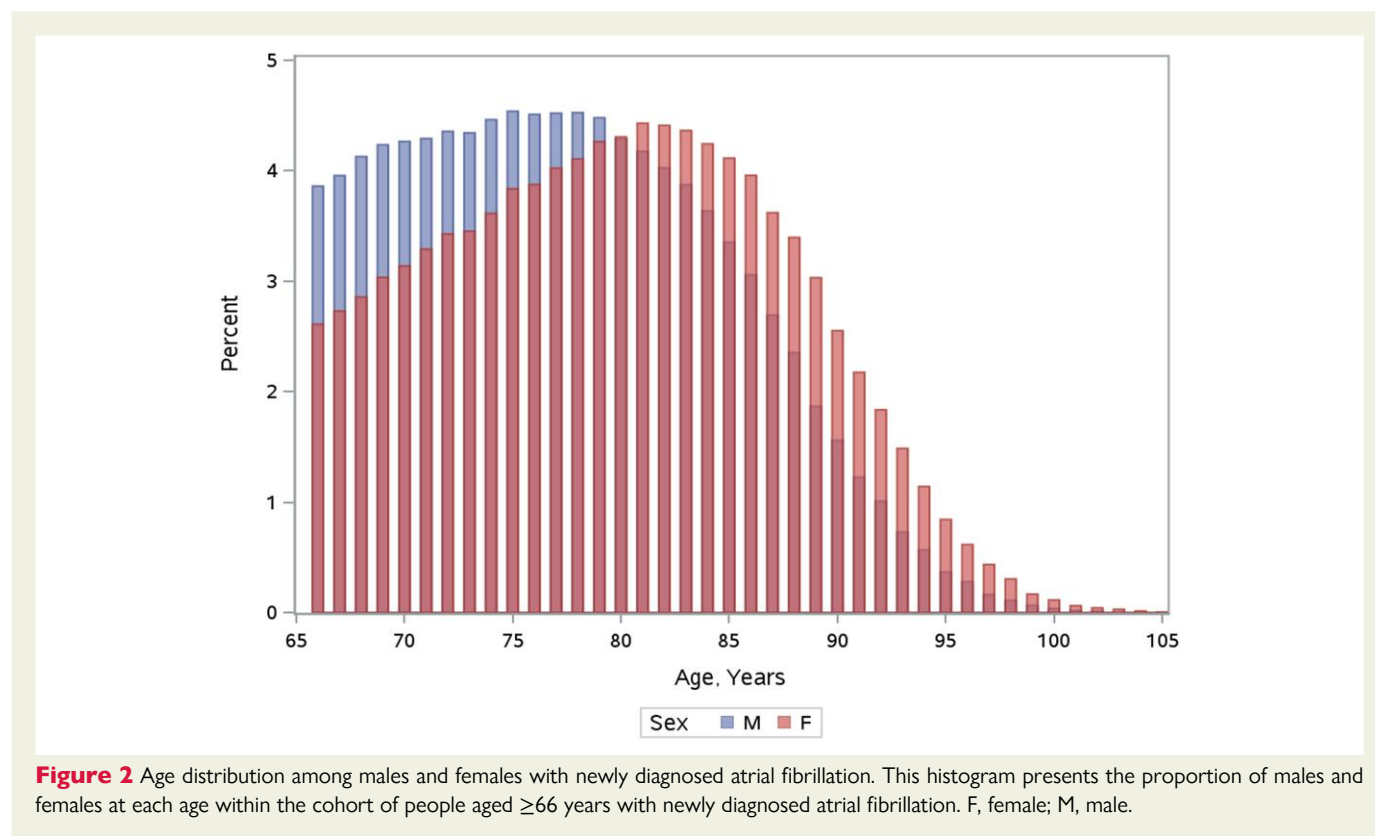
Standardized differences >0.1 are considered to represent meaningful differences between groups and have been highlighted in bold italics. The Q1–Q3 indicate the 25th and 75th percentiles.

AF, atrial fibrillation; eGFR, estimated glomerular filtration rate; LDL-C, low density lipoprotein cholesterol; TIA, transient ischaemic attack; DOAC, direct-acting oral anticoagulant (DOAC).

eGFR. Females were less likely to have LDL-C measurements (49.0% of females, 54.7% of males) or receive statins (48.3% of females; 59.6% of males) in the year before AF diagnosis, which was reflected in females having higher baseline LDL-C values than males [female median 2.2

(Q1–Q3 1.6–2.9 mmol/L); male median 1.9 (Q1–Q3 1.4–2.6 mmol/L)]. In the year before AF diagnosis, 20 032 (11.6%) females were assessed by a cardiologist compared to 30 669 (16.9%) males. The standardized difference for all comparisons reported above was  $\geq 0.1$ ; the





standardized differences between males and females for the remaining baseline characteristics was  $<0.1$ .

## Management after atrial fibrillation recognition

During the 2 years following the index date, 53 029 (30.7%) females were assessed by a cardiologist, compared with 66 938 (36.9%) males (standardized difference 0.13). Females were less likely to have been dispensed prescriptions for statins (54.2% vs. 65.3% of males) after AF diagnosis (standardized difference 0.23). There were smaller differences in receipt of echocardiography [109 861 (63.5%) females; 122 078 (67.3%) males; standardized difference 0.08] and no sex-based difference in the dispensation of anticoagulation overall (61.5% females vs. 61.4% males, standardized difference 0.004). However, there were higher rates of dispensation of low-dose DOACs to females (20.3%) than males (15.7%), with a standardized difference of 0.12. The analysis of DOAC dispensation in people unlikely to qualify for reduced dosing suggested that reduced dose DOACs are more likely dispensed to females in the absence of criteria for dose reduction. Details are provided in [Table 2](#).

## Relationship between sex and stroke

There were 7692 (2.2%) ischaemic strokes and 81 834 (23.1%) deaths in the 2 years following AF diagnosis. The age-standardized rate of ischaemic stroke was 1.4 (95% CI 1.3–1.4) per 100 person-years in females and 1.1 (95% CI 1.1–1.2) per 100 person-years in males. The age-standardized mortality rate was 10.7 (95% CI 10.6–10.9) per 100 person-years in females and 13.9 (95% CI 13.8–14.1) per 100 person-years in males. The cumulative incidence function curves for stroke by sex are provided in [Supplementary data online, Figure S1](#).

The HRs for stroke associated with female sex resulting from Models 1–3 are illustrated in [Figure 3](#). The HRs for other variables in Models 1–3 are presented in [Supplementary data online, Table S2](#). After adjustment in Model 1 (utilizing CHA<sub>2</sub>DS<sub>2</sub>-VASC variables, with age modelled as a binary variable), female sex was associated with significantly increased hazard of stroke (HR 1.27, 95% CI 1.21–1.32,  $P < .001$ ). There was a significant interaction between age and sex ( $P = .001$ ). When the analysis was repeated with an age-interaction term (Model 2), the HR associated with female sex was significantly higher than 1 in patients aged  $>70$  years but there was no significant difference by sex in stroke hazard among younger patients. In Model 3 (which further adjusted for markers of cardiovascular care and comorbidity), the HR was lower than Model 2 at all ages; female sex was only significantly associated with increased stroke hazard above the age of 80 years.

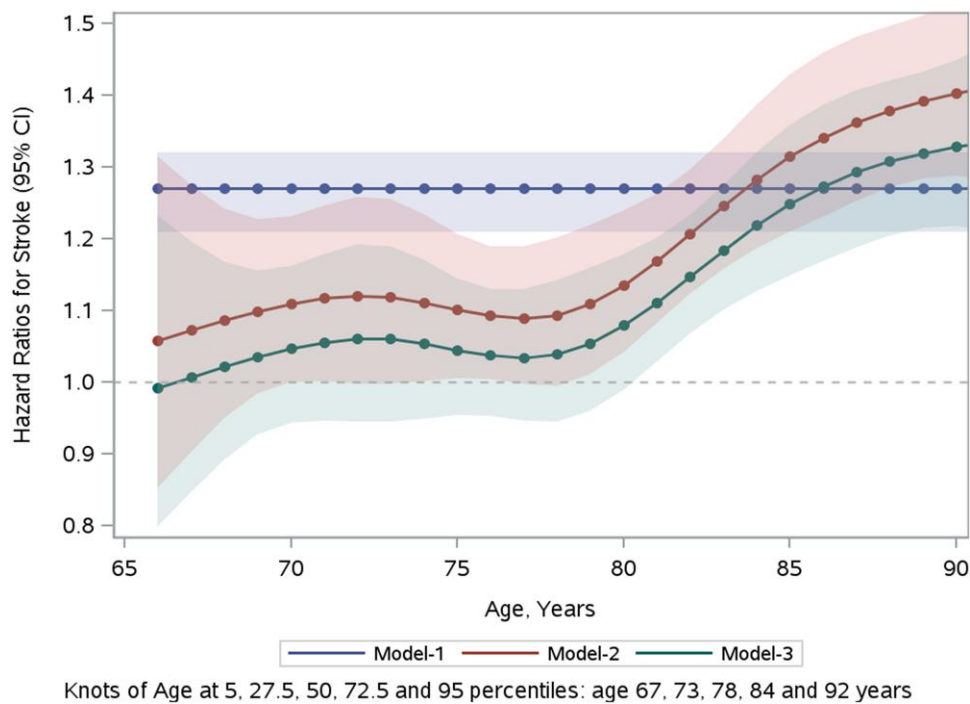
## Subset with blood pressure data

We identified a total of 7412 people [3686 (49.7%) female] with available BP measurements before or after AF diagnosis, of whom 6296 people [3164 (50.2%) female] had an available BP measurement in the EMRPC dataset within 365 days before AF diagnosis. Their baseline characteristics, compared with the remaining 347 958 patients, are shown in [Supplementary data online, Table S3](#). Participants with available BP data were less likely to live in neighbourhoods with higher material deprivation; there was no other meaningful difference in baseline characteristics. The median time between BP measurement and AF diagnosis was 42 (Q1–Q3 8–128) days. The median documented systolic BP before AF diagnosis was higher in females (median 130 mmHg; Q1–Q3 120–142 mmHg) than males (median 128 mmHg; Q1–Q3 116–140 mmHg), corresponding to a standardized difference of 0.17. There were no differences in diastolic BP

**Table 2** Analysis of direct oral anticoagulant dispensation in participants unlikely to qualify for reduced direct oral anticoagulant dosing

	Females	Males	Standardized difference	P-value
<b>People in cohort who are unlikely to qualify for reduced DOAC dosing regardless of weight</b>				
Sample size	n = 49 675	n = 67 628		
Warfarin	12 799 (25.8%)	18 876 (27.9%)	0.05	<.001
Full dose DOACs	17 930 (36.1%)	24 446 (36.1%)	0.001	.85
Reduced dose DOACs	7455 (15.0%)	8338 (12.3%)	0.08	<.001
<b>People in EMRPC dataset not meeting criteria for reduced dose DOACs</b>				
Sample size	n = 1323	n = 1679		
Warfarin	454 (34.3%)	565 (33.7%)	0.01	.7
Full dose DOACs	362 (27.4%)	471 (28.1%)	0.02	.67
Reduced dose DOACs	277 (20.9%)	267 (15.9%)	0.13	<.001

The upper half of the table describes anticoagulant dispensation in the 2 years after AF diagnosis in the subset of the cohort who would likely not qualify for reduced DOAC dosing regardless of weight—people aged <80 years with creatinine <133 μmol/L (1.5 mg/dL) and eGFR ≥50 mL/min as per the CKD-EPI equation. The bottom half of the table reports anticoagulant dispensation in the subset of participants in EMRPC with available weight data who had eGFR ≥50 mL/min and met <2 of the dose reduction criteria for apixaban (age ≥80 years, weight ≤60 kg, creatinine ≥133 μmol/L), as these people would be expected to qualify for the full dose of all DOACs. DOAC, direct-acting oral anticoagulant (DOAC).



**Figure 3** Adjusted hazard ratios for stroke associated with female sex. Model 1 includes the variables in the conventional CHA<sub>2</sub>DS<sub>2</sub>-VASc model: congestive heart failure, hypertension, age ≥75 years (doubled), diabetes, stroke (doubled), vascular disease, age 66 to 74 years, and sex category (female). Models 2 and 3 incorporated an interaction term between age and sex, with age handled as a continuous variable using restricted cubic splines utilizing five knots placed at the following percentiles: 5%, 27.5%, 50%, 72.5%, and 95%. Model 3 further accounted for baseline multimorbidity, markers of cardiovascular care as well as anticoagulation as a time-varying covariate.

(72 mmHg in both sexes). We also identified 6110 individuals [3036 (49.7%) female] who had available BP measurements within 2 years after AF diagnosis, taken at a median of 21 (Q1–Q3 5–78) days after AF diagnosis. The systolic BP after AF diagnosis remained significantly higher in females (128 mmHg, Q1–Q3 116–140 mmHg) compared to males (median 124 mmHg, Q1–Q3 111–137 mmHg, standardized difference 0.18), but there was no difference in diastolic BP (70 mmHg in both sexes).

## Discussion

This population-based study examined sex differences in age and cardiovascular care to determine their relationship to the higher stroke risk in females with AF. Despite having higher stroke incidence, females with AF were less likely to be assessed by cardiologists, get LDL-C testing, or receive statins. Females with AF also had higher LDL-C levels and higher BP than their male counterparts. The HR for stroke associated with female sex was age-dependent, such that it was only associated with increased stroke hazard at older ages. With adjustment for markers of cardiovascular care, the HR associated with female sex was substantially attenuated, such that female sex was only associated with increased stroke hazard at age >80 years (*Structured Graphical Abstract*).

Our findings indicate that age modifies the association between sex and stroke in AF, with female sex being independently associated with higher risk in those aged > 80 years, but not in younger people. Females tend to be older than men when diagnosed with AF, and the age-associated prevalence of cardiovascular risk factors increases at a faster rate in females than males.<sup>33,34</sup> The impact of older age may be compounded by the observation that older females are less likely to receive cardiovascular care than older males.<sup>33,35,36</sup> Although anticoagulation is the primary approach to stroke prophylaxis in AF, there remains a residual risk that may benefit from treatment of atherosclerotic risk factors.<sup>10</sup> We observed that females with AF were less likely to be treated with statins despite having higher LDL-C levels. Several observational studies report that statin use and lower LDL-C levels are associated with lower stroke risk in AF patients.<sup>37,38</sup> However, there are no randomized controlled trial data demonstrating benefit from statins specifically in the AF population. It may be that the lower stroke hazard associated with statin exposure and lower LDL-C levels indicate that they are markers of better cardiovascular care overall rather than directly causing a reduction in stroke risk.

Females were more likely to be first diagnosed with AF in the ED, which was associated with worse outcomes than diagnosis in other settings (see [Supplementary data online, Table S2](#)). A first diagnosis of AF in the ED was also associated with adverse outcomes in a prospective registry encompassing 47 countries with substantial regional variation.<sup>39</sup> We hypothesize that greater rates of initial AF diagnosis in the ED among females reflect less access to cardiovascular care among females, which is supported by the observation of lower rates of cardiologist assessment for females before and after AF diagnosis. Other studies have shown that cardiologist care after a new diagnosis of AF is associated with lower rates of stroke and other adverse outcomes.<sup>12,40</sup> Alternatively, the higher rates of AF diagnosis in the ED among females may relate to the higher symptom burden in females with AF.<sup>41</sup>

In exploratory analyses of people with available BP data, we observed that females had higher systolic BP than males before and after AF diagnosis. The CHA<sub>2</sub>DS<sub>2</sub>-VASc model treats hypertension as a dichotomous variable, but higher BP correlates with increased stroke risk in

AF.<sup>42–46</sup> One of the first models to predict stroke risk in AF was derived from the Framingham Heart Study.<sup>46</sup> In this model, every 10 mmHg increase in systolic BP was associated with a 10% relative increase in the rate of stroke. The association between higher BP and stroke risk continues to be reported in recent analyses with anticoagulated patients.<sup>42–45</sup> The effect of hypertension may be compounded by other stroke risk factors to a greater extent in females compared to men.<sup>47,48</sup> We were not able to incorporate BP data in our regression analyses due to the small size of the subset with available data. We hypothesize that the magnitude of HR will become even closer to the null in a model that accounts for actual BP levels in males and females.

## Limitations

The observational study design means that there remains the potential for residual confounding, including unmeasured sex-based treatment inequities. Given our reliance on administrative data, we could not account for important variables, including race, AF type/burden, and ejection fraction. We could not account for additional clinical factors which could have justified reduced dabigatran dosing in people aged 75–79 years despite having eGFR >50 mL/min. We did not have the requisite data to gauge the appropriateness of statin use or time in therapeutic range for warfarin-treated people. We could not account for aspirin use since it can be purchased over the counter in Ontario. However, aspirin is not efficacious neither is it recommended for stroke prevention in AF.<sup>49,50</sup> While the algorithms used to identify medical diagnoses have been validated, they are more specific than they are sensitive. It is possible that the sensitivity is even lower for older females than males since we observed that females have less cardiovascular care. If this were true, it would cause us to overestimate the HR associated with female sex, as we cannot adjust for HF, hypertension, diabetes, or vascular disease if they were unrecognized. Thus, we cannot exclude that the higher HR associated with female sex in people aged >80 years may represent insufficient adjustment due to detection bias in a population that may have even greater inequities in cardiovascular care. Finally, our results may be less generalizable outside the Canadian healthcare system, which is administered by a single payer and forbids out-of-pocket or private insurance payment for funded medically necessary services. The sex inequities in cardiovascular care may be accentuated in systems that have greater financial barriers to healthcare.

## Conclusion

Female patients with AF are more likely to be diagnosed in the ED than males, less likely to be assessed by cardiologists, less likely to receive statins, get LDL-C testing, and more likely to have higher systolic BP and LDL-C levels. The sex-specific difference in stroke hazard was attenuated after accounting for indicators of cardiovascular care. These data highlight the need to reduce sex-based inequities in cardiovascular care in older people with AF, as they may underlie the higher stroke risk observed among female patients.

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Health Postal Code Conversion File, which contains data copied under licence from ©Canada Post Corporation and Statistics Canada. Parts of this material are based on data and/or information compiled and provided by CIHI and the Ontario Ministry of Health. The analyses, conclusions, opinions, and statements expressed herein are solely those of the authors and do not reflect those of the funding or data sources (ICES, CIHI, or Ontario MOH/MLTC); no endorsement is intended or should be inferred. We thank IQVIA Solutions Canada Inc. for the use of their Drug Information File.

## Supplementary data

Supplementary data are available at *European Heart Journal* online.

## Declarations

### Disclosure of Interest

All authors declare no conflict of interest for this contribution.

### Data Availability

While data sharing agreements prohibit ICES from making the dataset publicly available, access may be granted to those who meet pre-specified criteria for confidential access, available at [www.ices.on.ca/DAS](http://www.ices.on.ca/DAS).

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### Ethical Approval

The use of data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a research ethics board.

### Pre-registered Clinical Trial Number

None supplied.

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