

Original Article

Nationwide Study of Sex Differences in Incident Heart Failure in Newly Diagnosed Nonvalvular Atrial Fibrillation

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In multivariable analysis, women with incident non-valvular atrial fibrillation (NVAF) without prior heart failure (HF) are at **8% increased risk** of HF hospitalization compared to men. This risk is attenuated by adjustment for medications.

- HF is a leading complication of NVAF and the presence of both conditions worsens prognosis.
- Independent sex-specific associations between NVAF and HF are unknown.

- Nationwide study of 68,909 newly-diagnosed NVAF patients ≥65 years old between April 2010 and March 2018 without a history of prior HF.
- Primary outcome: Incident HF hospitalization at 1 year.
- Secondary composite outcome: Incident HF hospitalization or all-cause mortality at 1 year.
- Other secondary outcomes: Temporal trends in outcomes over study period.

There was a significant 1.5% per year increase in HF hospitalizations for women over the study period but not for men.

Incident heart failure				Incident heart failure/all-cause mortality			
Model 1	HR(95% CI)	p		Model 1	HR(95% CI)	p	
Age 75+	1.22 (1.18-1.26)	<.001	---	Age 75+	1.11 (1.08-1.15)	<.001	---
Age 65-<75	0.95 (0.90-1.01)	0.094	---	Age 65-<75	0.91 (0.87-0.95)	<.001	---
Model 2	HR(95% CI)	p		Model 2	HR(95% CI)	p	
Age 75+	1.10 (1.06-1.13)	<.001	---	Age 75+	1.04 (1.01-1.07)	0.009	---
Age 65-<75	0.91 (0.86-0.96)	<.001	---	Age 65-<75	0.87 (0.83-0.91)	<.001	---

Hazard ratio (women vs men)

Cox proportional hazard regression Model 1 adjusted for age, comorbidities, socioeconomic status, geographic location, and electrical cardioversion. Model 2 adjusted for components of Model 1 and medications.

Women with incident NVAF without HF, particularly those ≥75 years, were more likely to suffer HF than men after adjusting for baseline risk and treatment strategies.

ABSTRACT

Background: Heart failure (HF) is a leading complication of non-valvular atrial fibrillation (NVAF), and the presence of both conditions worsens prognosis. Sex-specific associations between NVAF and outcomes focus on stroke; less is known about HF. We evaluated sex differences in incident HF in NVAF.

Methods: We identified adults age ≥ 65 years hospitalized for incident NVAF without prior HF from April 2010 to March 2018 in Canada. The primary outcome was incident HF hospitalization, with a secondary composite outcome of incident HF hospitalization or all-cause

RÉSUMÉ

Contexte : L'insuffisance cardiaque (IC) est une complication majeure de la fibrillation auriculaire non valvulaire (FANV), et la présence des deux affections assombrit le pronostic. Les associations entre la FANV et ses complications en fonction du sexe ont surtout porté sur l'AVC; on en connaît moins sur l'IC. Nous avons évalué les différences entre les sexes pour l'IC fortuite dans la FANV.

Méthodologie : Nous avons identifié des adultes de ≥ 65 ans, sans antécédents d'IC, hospitalisés pour une FANV fortuite entre avril 2010 et mars 2018 au Canada. L'hospitalisation à la suite d'une IC fortuite

mortality at 1 year. Cox proportional hazard regression models were constructed for the association between sex and outcomes, adjusting for age, comorbidities, socioeconomic status, cardioversion, and medications.

Results: Of 68,909 NVAF patients, 53.8% were women. Women had a higher rate of the primary outcome (30.0% vs 25.6%, $P < 0.001$) and the composite outcome (39.5% vs 36.6%, $P < 0.001$) than men. In multivariable analysis without adjusting for medications, there was an 8% increase risk of HF (95% confidence interval [CI] 1.05-1.11, $P < 0.001$) for women, which was attenuated when accounting for medication (hazard ratio [HR] 1.01, 95% CI 0.98-1.04). After full adjustment, women age ≥ 75 years were at higher risk of the primary outcome (HR 1.10, 95% CI 1.06-1.13, $P < 0.001$) and the composite outcome (HR 1.04, 95% CI 1.01-1.07, $P < 0.001$), compared with men, whereas there was a significantly lower risk for those age 65-75 years.

Conclusions: In this nationwide study of incident NVAF without HF, women age ≥ 75 years were more likely to develop HF or die than men. Strategies to prevent HF in older women with NVAF are needed.

constituait le critère d'évaluation principal, le critère d'évaluation secondaire composé comprenait les hospitalisations pour un épisode d'IC fortuite ou le décès toutes causes confondues à un an. Des modèles de régression à risques proportionnels de Cox ont servi à évaluer l'association entre le sexe et les résultats, après correction en fonction de l'âge, des comorbidités, de la situation socio-économique, de la cardioversion et de la médication.

Résultats : Le groupe étudié comptait 68 909 patients atteints de FANV dont 53,8 % étaient des femmes. Les femmes étaient plus nombreuses à répondre au critère d'évaluation principal (30,0 % vs 25,6 %, $p < 0,001$) et au critère d'évaluation composé (39,5 % vs 36,6 %, $p < 0,001$). Dans une analyse multivariée ne comportant aucune correction en fonction de la médication, une augmentation de 8 % du risque d'IC (intervalle de confiance [IC] à 95 % : 1,05-1,11, $p < 0,001$) a été notée chez les femmes. Cette augmentation se trouvait atténuée lorsque la médication était prise en compte (rapport des risques instantanés [RRI] : 1,01, IC à 95 % : 0,98-1,04). Après correction complète, les femmes de ≥ 75 ans ont été associées à un risque plus élevé d'atteindre le critère d'évaluation principal (RRI : 1,10, IC à 95 % : 1,06-1,13, $p < 0,001$) et le critère d'évaluation composé (RRI : 1,04, IC à 95 % : 1,01-1,07, $p < 0,001$) comparativement aux hommes; en revanche, le risque était significativement plus faible chez les femmes de 65-75 ans.

Conclusions : Dans cette étude nationale sur la FANV fortuite sans IC, les femmes de ≥ 75 ans étaient plus susceptibles de développer une IC ou de décéder que les hommes d'où la nécessité de mettre en place des stratégies de prévention de l'IC chez les femmes plus âgées atteintes de FANV.

Atrial fibrillation (AF) is a critical health and economic issue¹ that will only worsen, as it is increasing in prevalence. Preventing AF-related complications is therefore a priority. Important sex-specific associations between AF and outcomes have been described but focus mainly on stroke and thromboembolism.² Less evidence is available on the impact of sex on the relationship between AF and heart failure (HF), which is being recognized increasingly as a leading sequela of AF, particularly in older patients.³

The few studies that have evaluated sex-specific differences in HF among individuals with AF have found mixed results. In the Framingham Heart study⁴ and the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) registry,⁵ sex was not associated with developing HF, whereas in the Prevention of Thromboembolic Events – European Registry (PREFER) in AF study, women had 20% lower odds of developing HF.⁴⁻⁶ Most of these studies had small sample sizes, had women representing $< 40\%$ of the

cohort, and included only prevalent AF; none excluded patients with prior history of HF. Furthermore, no study has evaluated whether the incidence of AF-related HF is changing over time for women and men over a contemporary time period.

Given that the concomitant presence of AF and HF worsens morbidity, mortality, and cost beyond the level of these for each condition individually,^{7,8} a better understanding of the susceptibility for HF in women and men may offer opportunities to better tailor treatment strategies. Accordingly, we sought to examine sex-specific differences in the rates of incident HF hospitalizations at 1 year among patients with a new diagnosis of nonvalvular AF (NVAF) and no prior HF history. We also examined sex-specific differences in the rate of incident HF hospitalization or all-cause mortality at 1 year and temporal changes in outcomes over the study period. Finally, we evaluated the association between sex and outcomes after adjustment for baseline risk factors and treatments, including medications.

Methods

Study design and data source

We conducted a retrospective cohort study using longitudinal administrative data from all of Canada (excluding the province of Quebec) from between April 1, 2010 and March 31, 2018. The Canadian Institute for Health Information (CIHI) maintains a national repository of health

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Ethics Statement: This study conformed to the principles outlined in the Declaration of Helsinki and was approved by the University of Alberta Health Research Ethics Board (Pro00083729), including waiving the need for individual patient informed consent.

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See page 708 for disclosure information.

administrative data from provincial health authorities. We used the Discharge Abstract Database (DAD), which contains complete data for all inpatient acute care hospitalizations and surgical procedures, and the National Prescription Drug Utilization Information System (NPDUIS), which contains prescription claims-level data.

Study cohort

We identified all adults aged 65 years or older hospitalized with a new diagnosis of NVAF using the *International Classification of Diseases—10th revision* (ICD-10) code I48 in the primary diagnosis field, excluding patients with valvular disease using ICD and Canadian Classification of Health Interventions procedure codes (Supplemental Table S1).⁹ To identify an incident AF cohort, we excluded patients with a hospitalization for NVAF in the 5 years prior to the study period. In the case of multiple hospitalizations over the study period, the first hospitalization with NVAF was defined as the index hospitalization. To ensure no prior history of HF, we excluded patients with HF documented in any diagnosis field in the 5 years preceding the index NVAF hospitalization.

Demographics and clinical data

Demographics and data on pre-existing comorbid conditions, specifically components of CHADS₂ (Congestive Heart Failure, Hypertension, Age [≥ 75 Years], Diabetes, Stroke/Transient Ischemic Attack [doubled]) and CHA₂DS₂-VASc (Congestive Heart Failure or Left Ventricular Dysfunction, Hypertension, Age ≥ 75 Years [doubled], Diabetes, Stroke/Transient Ischemic Attack [doubled], Vascular Disease, Age [65-74 years], Sex [Female]) score were obtained from the DAD if the condition was present in the 5 years prior to the incident diagnosis of NVAF (Supplemental Table S1).^{10,11} The urban/rural location was established based on patients' residential postal codes from Statistics Canada dissemination areas. Socioeconomic effects were estimated using the income quintile derived using the Postal Code Conversion File from Statistics Canada.¹² Electrical cardioversions were recorded from the DAD using Canadian Classification of Health Interventions procedure codes if documented within 30 days of NVAF diagnosis (Supplemental Table S1). Baseline prescription data were obtained from the NPDUIS and were available for all provinces except Quebec and Nova Scotia using Anatomical Therapeutic Chemical Classification System codes if filled within 30 days following the index NVAF diagnosis (Supplemental Table S2).

Outcomes

The primary outcome was an incident HF hospitalization at 1 year following a new NVAF diagnosis. The outcome was defined as HF present in a secondary diagnosis field at index AF hospitalization, or primary or secondary HF in any subsequent hospitalization. The composite outcome was incident HF hospitalization or all-cause mortality at 1 year. All-cause mortality consisted of in-hospital and out-of-hospital death. In-hospital death was identified from the DAD. Out-of-hospital mortality was identified using an algorithm incorporating the NPDUIS database. If, after 150 days after the last dispensation days' supply ran out (all drugs), there was still

follow-up time remaining (until March 31, 2019), death was assumed to have occurred at the last dispensation date. Secondary outcomes included temporal trends in outcomes over the study period.

Statistical analysis

Results are presented as median with interquartile range, and mean with standard deviation, for continuous variables, and as count with percentages for categorical variables. Comparison between women and men was performed using the χ^2 test, the 2-sample *t*-test, and the Mann-Whitney *U* test, as appropriate. Incidences of outcomes were calculated and assessed for temporal trends using the Cochrane Armitage test and a negative binomial regression model. The trend in outcomes over time was adjusted for potential confounders of age, fiscal year, hospital type, residential area, income quintile, diabetes, hypertension, vascular disease, stroke/transient ischemic attack/systemic embolism, chronic renal disease, and electrical cardioversion.¹³⁻¹⁵ Outcomes were analyzed using 3 multivariable Cox proportional hazard regression models, as follows: unadjusted; age-adjusted model 1 (age [continuous], hospital type, residential area, income quintile, diabetes, hypertension, vascular disease, stroke/transient ischemic attack/systemic embolism, chronic renal disease, and electrical cardioversion); and model 2, which included all the covariates in model 1 and baseline medications. Adjustment was performed by medication class—antiarrhythmics, beta-blockers, renin-angiotensin-aldosterone system inhibitors, nondihydropyridine calcium-channel blocker, diuretics, oral antihyperglycemics, adenosine diphosphate antagonists, digoxin, and statins. Patients with incomplete data ($n = 779$) were not included in the multivariable analysis. We excluded patients from Nova Scotia ($n = 2374$) from the analysis because medication data were not available. We presented HF hospitalization with cumulative incidence curves, including death as a competing event, and performed a cause-specific multivariable Cox proportional hazard regression model censoring death to get the underlying risk of event. A 2-sided *P* value of < 0.05 was considered statistically significant. All analyses were performed in SAS 9.4 (SAS Institute, Cary, NC).

Ethics

This study conformed to the principles outlined in the *Declaration of Helsinki* and was approved by the University of Alberta Health Research Ethics Board (Pro00083729), including waiving the need for individual patient informed consent.

Results

Demographics

Among our cohort of 68,909 patients ≥ 65 years old with incident NVAF without prior HF, 53.8% were women. Compared to men, women were older, more likely to have hypertension and stroke/systemic embolism, and less likely to have diabetes, peripheral vascular disease, and coronary artery disease (CAD; Table 1). Women were less likely than men to have electrical cardioversion, but they had similar rates of antiarrhythmic medication prescription. Women were more

Table 1. Baseline characteristics

Variable	Women	Men	Total	<i>P</i>
Number of patients	37,048 (53.8)	31,861 (46.2)	68,909 (100)	
Age, y at AF diagnosis, mean (SD)	80.2 (± 8.3)	76.7 (± 7.8)	78.6 (± 8.3)	< 0.001
Hospital type	142 (0.4)	157 (0.5)	299 (0.4)	< 0.001
Academic	10,239 (27.6)	10,348 (32.5)	20,587 (29.9)	
Community	26,667 (72.0)	21,356 (67.0)	48,023 (69.7)	
Residential area	169 (0.5)	168 (0.5)	337 (0.5)	< 0.001
Rural/remote	8450 (22.8)	8061 (25.3)	16,511 (24.0)	
Urban	28,429 (76.7)	23,632 (74.2)	52,061 (75.6)	
Income quintile	251 (0.7)	230 (0.7)	481 (0.7)	< 0.001
First (highest)	9300 (25.1)	6410 (20.1)	15,710 (22.8)	
Second	8305 (22.4)	6652 (20.9)	14,957 (21.7)	
Third	7263 (19.6)	6501 (20.4)	13,764 (20.0)	
Fourth	6043 (16.3)	5790 (18.2)	11,833 (17.2)	
Fifth (lowest)	5886 (15.9)	6278 (19.7)	12,164 (17.7)	
CHADS ₂				
Mean (SD)	1 (± 1)	1 (± 1)	1 (± 1)	< 0.001
Median (IQR)	1 (1, 2)	1 (1, 2)	1 (1, 2)	< 0.001
CHA ₂ DS ₂ -VASc				
Mean (SD)	3 (± 1)	3 (± 1)	3 (± 1)	< 0.001
Median (IQR)	3 (2, 3)	2 (2, 3)	3 (2, 3)	< 0.001
Comorbidities				
Diabetes	7417 (20.0)	7728 (24.3)	15,145 (22.0)	< 0.001
Hypertension	16,377 (44.2)	12,457 (39.1)	28,834 (41.8)	< 0.001
Coronary artery disease	4366 (11.8)	5670 (17.8)	10,036 (14.6)	< 0.001
Peripheral vascular disease	768 (2.1)	1038 (3.3)	1806 (2.6)	< 0.001
Stroke/TIA/systemic embolism	1811 (4.9)	1362 (4.3)	3173 (4.6)	< 0.001
Treatment				
Electrical cardioversion	2771 (7.5)	4472 (14.0)	7243 (10.5)	< 0.001
Medication, patients*	35,717	30,818	66,535	
Beta blocker	17,009 (47.6)	12,829 (41.6)	29,838 (44.8)	< 0.001
ACEi/ARB	9443 (26.4)	7597 (24.7)	17,040 (25.6)	< 0.001
MRA	996 (2.8)	1036 (3.4)	2032 (3.1)	< 0.001
Digoxin	5088 (14.2)	3288 (10.7)	8376 (12.6)	< 0.001
Nondihydropyridine CCB	5355 (15.0)	3349 (10.9)	8704 (13.1)	< 0.001
Oral antihyperglycemics	2357 (6.6)	2413 (7.8)	4770 (7.2)	< 0.001
Statin	7,047 (19.7)	6,701 (21.7)	13,748 (20.7)	< 0.001
ADP receptor antagonists	808 (2.3)	802 (2.6)	1610 (2.4)	0.004
Diuretics	9353 (26.2)	6380 (20.7)	15,733 (23.6)	< 0.001
OAC	15,493 (43.4)	11,867 (38.5)	27,360 (41.1)	< 0.001
Warfarin	7428 (20.8)	6178 (20.1)	13,606 (20.4)	0.017
DOAC	8065 (22.6)	5689 (18.5)	13,754 (20.7)	< 0.001
Antiarrhythmics	3928 (11.0)	3657 (11.9)	7585 (11.4)	< 0.001
Sotalol	668 (1.9)	775 (2.5)	1443 (2.2)	< 0.001
Flecainide	253 (0.7)	145 (0.5)	398 (0.6)	< 0.001
Propafenone	510 (1.4)	411 (1.3)	921 (1.4)	0.30
Amiodarone	2551 (7.1)	2371 (7.7)	4922 (7.4)	0.007

Values displayed are n (%), unless otherwise indicated. "Antiarrhythmics" refers to Vaughan-Williams class I or III antiarrhythmics used for an antiarrhythmic indication. Data were unavailable for some patients: hospital type (n = 299), residential area (n = 337), and income quintile (n = 481).

ACE, angiotensin-converting enzyme; ACE-i, ACE inhibitor; ADP, adenosine diphosphate; AF, atrial fibrillation; ARB, angiotensin receptor blocker; CAD, coronary artery disease; CCB, calcium-channel blocker; CHADS₂, Congestive Heart Failure, Hypertension, Age ≥ 75 Years, Diabetes, Stroke/Transient Ischemic Attack [doubled]; CHA₂DS₂-VASc, Congestive Heart Failure or Left Ventricular Dysfunction, Hypertension, Age ≥ 75 Years [doubled], Diabetes, Stroke/Transient Ischemic Attack [doubled], Vascular Disease, Age [65-74 years], Sex [Female]; DOAC, direct oral anticoagulant; IQR, interquartile range; MRA, mineralocorticoid receptor antagonist; OAC, oral anticoagulation; PVD, peripheral vascular disease; SD, standard deviation; TIA, transient ischemic attack.

* Excluding 2374 patients from Nova Scotia, due to unavailability of medication data.

likely than men to be prescribed both warfarin and direct oral anticoagulants.

Incident HF hospitalization

Overall, 28.0% of the cohort had a hospitalization for incident HF. The primary outcome occurred more often in women than men (30.0% vs 25.6%, *P* < 0.001; Fig. 1). Over the study period, the 1-year incidence of HF hospitalizations increased by 1.5% per year for women (27.4% to 30.8%, *P* < 0.001 for trend) and by 0.9% per year for men (24.0% to 25.6%, *P* = 0.063; Fig. 2).

The association between sex and outcomes is shown in Table 2. In age-adjusted analysis, women had a 7% increase in the risk of incident HF, compared with that for men. In multivariable analysis without adjusting for medication (model 1), the increased risk of HF remained for women. When medications were accounted for, the difference in HF risk between men and women was no longer significant (hazard ratio [HR] 1.01, 95% confidence interval [CI] 0.98-1.04), *P* = 0.51). A significant interaction was found between age and sex (*P* < 0.001) prompting further evaluation of outcomes by sex categories (Fig. 3). In model 1, we found a

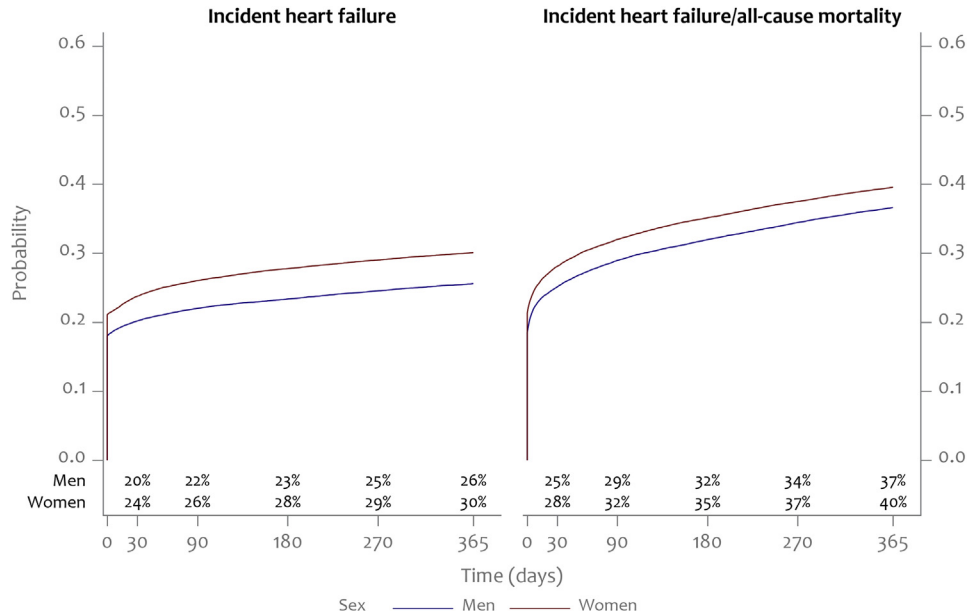


Figure 1. Incidence of (left) the primary outcome of heart failure hospitalization and (right) the composite outcome of heart failure hospitalization or all-cause mortality over time.

22% increased HF risk for women age ≥ 75 years, which remained elevated after full adjustment (model 2; HR 1.10, 95% CI 1.06-1.13, $P < 0.001$). Women age 65-74 years had a lower HF risk, compared to that for men (HR 0.91, 95% CI 0.86-0.96, $P < 0.001$).

Chronic kidney disease, diabetes, increasing age, lower income, and CAD were associated with increased HF risk, and electrical cardioversion was associated with an 11% lower risk of HF hospitalization (HR 0.89, 95% CI 0.85-0.94, $P < 0.001$; Supplemental Table S2).

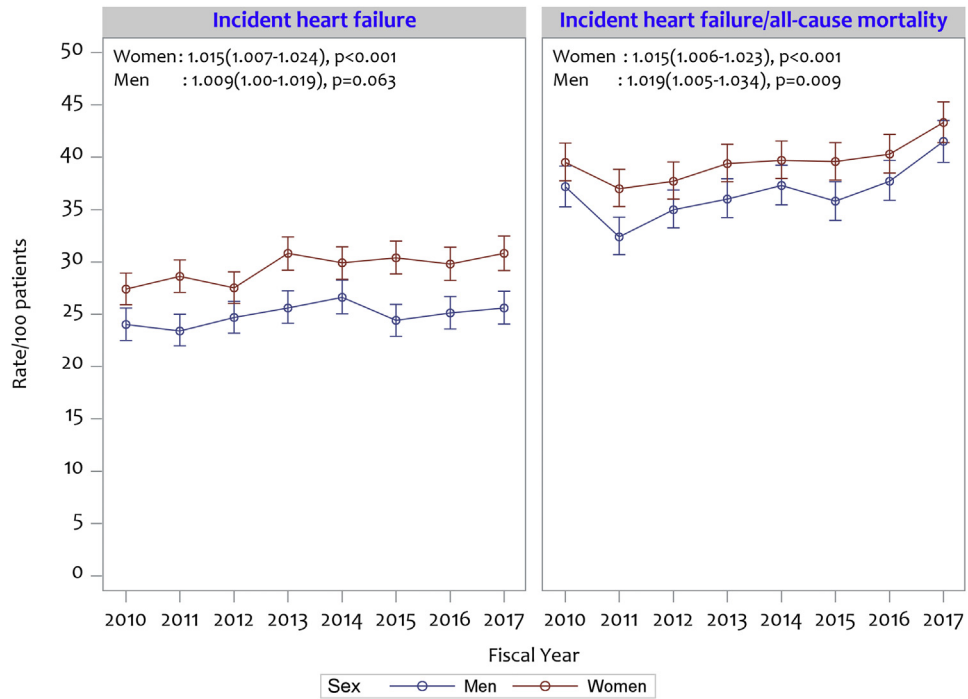


Figure 2. Rate of (left) the primary outcome of heart failure hospitalization and (right) the composite outcome of heart failure hospitalization or all-cause mortality over time.

Table 2. Unadjusted and adjusted hazard ratios of outcomes for women vs men

Adjustment	Women vs men	
	Incident HF	Incident HF/ All-cause mortality
	HR and 95% CI	HR and 95% CI
Unadjusted	1.20 (1.17–1.23); $P < 0.001$	1.10 (1.08–1.13); $P < 0.001$
Age-adjusted	1.07 (1.04–1.10); $P < 0.001$	0.99 (0.97–1.01); $P = 0.32$
Model 1*	1.08 (1.05–1.11); $P < 0.001$	1.00 (0.97–1.02); $P = 0.76$
Model 2†	1.01 (0.98–1.04); $P = 0.48$	0.95 (0.93–0.97); $P < 0.001$

The interaction between age and sex was significant, $P < 0.001$.

CI, confidence interval; HF, heart failure; HR, hazard ratio.

* Model 1 was adjusted for age (continuous), hospital type, residential area, income quintile, diabetes, hypertension, vascular disease, stroke/transient ischemic attack/systemic embolism, chronic renal disease, and electrical cardioversion.

† Model 2 included all the covariates in model 1 and baseline medications.

Incident HF hospitalization or all-cause mortality

Overall, 38.2% of the cohort had the composite outcome at 1 year. The composite outcome occurred more often in women than men (39.5% vs 36.6%, $P < 0.001$; Fig. 1). The 1-year incidence of the composite outcome increased by 1.5% annually for women (39.5% to 43.3%, $P < 0.001$ for trend) and by 1.9% annually for men (37.2% to 41.5%, $P = 0.009$ for trend; Fig. 2).

In both age-adjusted analysis and multivariable analysis without adjusting for medication (model 1), the risk of the composite outcome was similar for women and men. When medications were adjusted for (model 2), women experienced a 5% lower risk of the composite outcome, compared with that for men (HR 0.95, 95% CI 0.93–0.97, $P < 0.001$; Table 2). A significant interaction occurred between age and sex ($P < 0.001$), necessitating further evaluation (Fig. 3). In model 1, women ≥ 75 years old had an 11% increased risk of developing the composite outcome, compared with that for men of the same age, which persisted after full adjustment (model 2; HR 1.04, 95% CI 1.01–1.07, $P = 0.009$). Women 65–75 years old were found to have a 13% lower risk of the composite outcome, compared with that for men (HR 0.87, 95% CI 0.83–0.91, $P < 0.001$; Fig. 3).

We found that increasing age, diabetes, CAD, peripheral vascular disease, and chronic kidney disease were significantly

associated with an increased risk of the composite outcome, whereas electrical cardioversion, antiarrhythmics, beta-blockers, non-dihydropyridine calcium-channel blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blocker, oral antihyperglycemic agents, statins, and adenosine diphosphate antagonists were associated with lower risk (Supplemental Table S3).

Discussion

In this nationwide study of patients with newly diagnosed NVAF and no prior history of HF, we found higher rates of incident HF and HF or all-cause mortality in women than in men. Over a contemporary study period, we found a significant increase in HF for women and a significant increase in HF or all-cause mortality among both sexes. The increased risk for HF for women, compared with that for men, was attenuated after a comprehensive adjustment for baseline risk and medication. However, we found that women ≥ 75 years old were at increased risk of HF alone, and a composite of HF and death, than were men of the same age, even after adjustment for these factors.

Our study is novel in reporting contemporary temporal trends in incident HF and composite endpoint by sex. We found that rates of outcomes increased by 1.5% per year for women and 1.9% for men for the composite endpoint, from 2009 to 2017. A prior retrospective study of incident AF patients ($n = 3288$), on data from 1980–2000 in Olmstead County, found that calendar year was not a significant predictor of age- and sex-adjusted incidence of new HF hospitalization.¹⁶ The patients from Olmstead County had a lower comorbidity burden, compared to that of our cohort, as both outpatients and inpatients were included and incidence according to sex was not assessed. We have previously shown, using the same national database, that over similar study years, the comorbidity burden among NVAF patients (CHADS₂ score ≥ 2 from 51.6% to 54.3%, P value for trend < 0.0001) has increased over time. This finding suggests that the increasing HF hospitalization rates over time seen in our study may be due to a progressively more comorbid population.¹³

Prior retrospective studies evaluating sex-specific differences in HF in NVAF patients have found varying results. Several prior observational studies^{5,17–19} reported no sex-based differences in HF. When we restricted our analysis to those



Figure 3. Unadjusted and adjusted hazard ratios (HRs) of 1-year incidence of outcomes for women vs men, stratified by age category. CI, confidence interval.

with incident NVAF and no prior HF, we similarly found that incident HF risk did not differ between men and women. Our results stand in contrast to those of the European Registry in Atrial Fibrillation study, which found that women had a lower risk of HF hospitalization than men, but only when analyses were adjusted for age and country.⁶ We provide the novel finding that, despite full analyses adjustment, women at an older age (≥ 75 years) have increased risk of incident HF, and the composite endpoint, compared to that for men of the same age.

Several reasons are possible for an increased risk of incident HF and mortality in older women. Older women in particular are prone to worsening diastolic dysfunction, which makes their ventricles more reliant on active ventricular filling via the atrial kick.²⁰ Loss of the atrial kick due to AF may severely impair ventricular filling, leading to HF with preserved ejection fraction. Despite having a greater symptom burden and lower quality-of-life scores,^{21,22} women with AF have been found in previous studies to be less likely to be managed with a rhythm control strategy than men.^{5,6,17,23} In addition, women were found to be less likely than men to undergo electrical cardioversion and more likely to be prescribed digoxin.^{5,23}

In our study, women had a higher level of use of antiarrhythmic drugs but were less likely to undergo electrical cardioversion, compared with men. There are several possible explanations, which may explain in part the treatment disparities between female and male patients with respect to antiarrhythmic use and electrical cardioversion. First, we found that men had a higher rate of CAD, and given that Vaughan-Williams class Ic agents are contraindicated in this setting, this may be why medications in this class were less likely to be prescribed. Second, prior studies have shown that rate-control strategies are often pursued in women; our finding that digoxin use was higher for women may be consistent with that practice pattern.⁶ A preference for a rate-control strategy may also be a reason that fewer electric cardioversions were observed in women. Third, data suggest that women with AF are less likely to undergo invasive procedures.^{6,24} Women may have a lower success rate with catheter ablation²⁵ and higher complication rates,²⁶ which may further rationalize physician decisions with respect to rate control or rhythm control using antiarrhythmic drugs. Further studies are needed to determine whether older women would benefit from aggressive rhythm-control strategies to prevent HF.

Limitations

Our analysis has limitations that deserve attention. First, we were not able to determine the type of AF (paroxysmal, persistent, or permanent). Second, our administrative data did not allow for ascertainment of the type of HF (preserved, mid-range, or reduced ejection fraction). Administrative data using ICD codes were used to establish diagnosis of NVAF, HF, and comorbidities, which could be subject to misclassification or under-coding. However, these ICD codes have been previously used to accurately identify patients with AF and HF.²⁷⁻²⁹

The patients in our study represent a subset of the NVAF patients who were admitted and may not be representative of all NVAF patients. Decisions regarding admission may reflect

numerous factors, including comorbidity burden, local practice patterns, and geographic factors. Our study focused on patients who were hospitalized with incident HF, and it does not capture all HF events that may have occurred, specifically those in the outpatient setting. HF events may be misdiagnosed, as they were identified using administrative data rather than with natriuretic peptides and/or imaging. However, a systematic review of validated methods for identifying HF using administrative data found a high positive predictive value, ranging from 79% to 96%, when HF was defined as occurring in any diagnostic position.²⁹ We were unable to abstract details regarding severity of comorbidities from the databases. We are not able to account for patient noncompliance, discontinuation due to side effects, or prescriptions being filled outside of Canada.

We recognize that the death-date algorithm is a new approach to assessing all-cause mortality. We validated the death-date algorithm in NVAF patients age ≥ 65 years using Alberta health data (vital statistics, DAD, and the pharmaceutical information network) and found, using a 150-day prescription gap, a sensitivity and specificity of 95% and 96%, respectively, and the log-rank χ^2 statistic was 3.26. The bias in all-cause survival at 1 and 3 years of follow-up was 1%. Specific dosage data were not available. We were unable to capture AF procedures such as pulmonary vein isolation or “pace and ablate” strategies, as outpatient procedures are not captured in the DAD, that may influence HF development. Data regarding the adequacy of ventricular rate control were not available. Lastly, our results may not be generalizable to other jurisdictions. Our finding that older women, compared with men, had a worse prognosis may be the result of any of the limitations identified above, such as, differences in the type and extent of comorbidities, caregiver philosophy with respect to admission and treatment, and differences in the specific therapies administered.

Conclusions

In this large, nationwide study of patients with incident NVAF without prior HF, we found higher rates of HF and of HF or death in women than in men. After a comprehensive adjustment of baseline risk, no significant sex-based difference was found in the risk of either HF or HF or death. However, despite analysis adjustment, women age ≥ 75 years have an elevated risk of both HF and HF or death, compared with that for men of the same age. Further research is needed to confirm potential hypotheses to explain this sex difference, including evaluation of whether targeted treatment of AF, such as rhythm-control strategies, and closer follow-up may reduce the HF risk among older women with NVAF.

Data Availability Statement

The data underlying this article were provided by the Canadian Institute of Health Information (CIHI), by permission. Data will be shared on request to the corresponding author, with permission from CIHI.

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Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

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