CJC Open 4 (2022) 65–74

Original Article

A Population-Based Study of Unexplained/Lone Atrial Fibrillation: Temporal Trends, Management, and Outcomes

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ABSTRACT

Background: Previous studies on lone/unexplained atrial fibrillation and atrial flutter (AF) did not exclude patients with contemporary secondary AF triggers. We characterized unexplained AF using a strict definition, and compared it to secondary AF.

Methods: In this population-based study, unexplained AF was defined by the lack of any identifiable triggering medical/surgical diagnosis. Comparisons by AF type (unexplained vs secondary), age-of-onset ($\leq$ / $>$ 65 years), and sex were undertaken. Data were acquired by linking 6 population databases maintained by the Alberta Ministry of Health over a 9-year period (April 2006 to March 2015). The primary

RÉSUMÉ

Contexte : Les études précédentes sur le flutter auriculaire et la fibrillation auriculaire (FA) idiopathiques/inexpliqués n'excluaient pas les patients présentant des déclencheurs contemporains de FA secondaire. Nous avons caractérisé la FA inexpliquée en utilisant une définition stricte, et l'avons comparée à la FA secondaire.

Méthodologie : Dans cette étude basée sur une population, la FA inexpliquée a été définie par l'absence de tout diagnostic médical/chirurgical de déclencheur identifiable. Des comparaisons par type de FA (inexpliquée vs secondaire), par âge d'apparition ($\leq$ / $>$ 65 ans) et par sexe ont été effectuées. Les données ont été acquises en reliant

Atrial fibrillation and atrial flutter (AF is used to designate the combined incidence—ie, either one or both, although these are not specified separately) are common arrhythmias that affect ~2% of the population and lead to substantial morbidity and mortality, mainly due to an increased risk of stroke.[1] Acquired, environmental, and genetic factors play a role in the pathogenesis of AF,[1,2] including male sex, advancing age, and family history.[2,3] In most, AF occurs "secondary" to a comorbid condition, either cardiac in origin, such as coronary artery disease and heart failure, or extracardiac in nature, such as infectious and chronic pulmonary disease.[1] However, in a proportion of predominantly young individuals, AF develops as a primary disorder without an identifiable trigger, often termed unexplained, idiopathic, or lone AF.[4,5] Although event-free survival is better in unexplained AF,[3,5] its definition with respect to age of onset and comorbidity burden is inconsistent.[6] For example, the Framingham Heart Study of unexplained AF included patients with high blood pressure and advanced age,[4] both now considered to be strong risk factors for secondary AF.[7] Understanding unexplained AF is important because diagnostic/screening approaches, therapeutic recommendations, and natural history can differ from those for acquired/secondary AF.[6] In this study, we characterized unexplained AF in a dataset from a large population, using a stringent

Received for publication July 22, 2021. Accepted September 6, 2021.

Ethics Statement: The research reported has adhered to the relevant ethical guidelines.

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Please see page 73 for disclosure information.

https://doi.org/10.1016/j.cjco.2021.09.006

composite outcome of stroke, transient ischemic attack, thromboembolism, and/or death was assessed.

Results: There were 33,150 incident AF diagnoses identified, including 1145 patients (3.5%) with unexplained AF, 931 (81.2%) of whom were aged $\leq$ 65 years (2.8% of diagnoses, and 79% male). Patients with unexplained AF less often received rate/rhythm-control drugs ($P < 0.0001$), but they more often underwent electrical cardioversion ($P < 0.0001$) vs secondary AF patients. Men were younger at unexplained AF diagnosis (45 [interquartile range: 34-59] vs 58 [interquartile range: 40-69] years; $P < 0.001$). After adjusting for age at diagnosis, there were no sex-based differences in the primary outcome. Event-free survival in young unexplained AF (age $\leq$ 65 years) was 99.4% at 1 year and 98.3% at 3 years. At 3 years, hospitalization(s)/emergency visit(s) for noncardiovascular reasons and for AF occurred in 56.6% and 23.8% of these patients, respectively.

Conclusions: Using a strict contemporary definition of unexplained AF, this study shows that the condition is rare, predominantly male, and has excellent event-free survival. However, the high rate of acute hospital utilization after diagnosis is concerning.

six bases de données de population maintenues par le ministère de la Santé de l'Alberta sur une période de neuf ans (avril 2006 à mars 2015). Le paramètre d'évaluation principal comprenant l'accident vasculaire cérébral (AVC), l'accident ischémique transitoire, la thromboembolie et/ou le décès a été évalué.

Résultats : Au total, 33 150 diagnostics de FA ont été recensés, dont 1 145 patients (3,5 %) présentant une FA inexpliquée, parmi lesquels 931 (81,2 %) étaient âgés de $\leq$ 65 ans (2,8 % des diagnostics, et 79 % d'hommes). Les patients atteints de FA inexpliquée ont moins souvent reçu de médicaments pour contrôler la fréquence ou le rythme cardiaque ($p < 0{,}0001$), mais ils ont plus souvent subi une cardioversion électrique ($p < 0{,}0001$) par rapport aux patients atteints de FA secondaire. Les hommes étaient plus jeunes au moment du diagnostic d'une FA inexpliquée (45 [intervalle interquartile : 34 à 59] vs 58 [intervalle interquartile : 40 à 69] ans; $p < 0{,}001$). Après un ajustement pour l'âge au moment du diagnostic, il n'y avait pas de différence entre les sexes quant au paramètre d'évaluation principal. La survie sans événement chez les patients jeunes ayant présenté une FA inexpliquée (âge $\leq$ 65 ans) était de 99,4 % à un an, et de 98,3 % à trois ans. À trois ans, une ou plusieurs hospitalisations/consultations à l'urgence pour des raisons non cardiovasculaires et pour une FA sont survenues chez 56,6 % et 23,8 % de ces patients, respectivement.

Conclusions : En utilisant une définition contemporaine stricte de la FA inexpliquée, cette étude montre que cette affection est rare, majoritairement masculine, et qu'elle est associée à une excellente survie sans événement. Cependant, le taux élevé d'utilisation de soins actifs dans les hôpitaux après le diagnostic est préoccupant.

contemporary definition, which accounted for a multitude of potentially AF-predisposing comorbidities, and compared it to secondary AF.

Methods

Study population

We included all patients with an incident diagnosis of AF between April 1, 2006 and March 31, 2015 (the 2006-2014 fiscal years) evaluated in the single-payer healthcare system across the entire province of Alberta. The first diagnosis of AF was identified from inpatient and ambulatory databases using the validated[8,9] *International Classification of Diseases,* 9th edition (ICD9: code 427.3) and 10th edition (ICD10: code I48) codes from the primary diagnostic fields during the study period. Prevalent AF cases were excluded, defined as a preexisting AF diagnosis in any database (inpatient, ambulatory, and claims) from 1994 onward to current diagnosis. All patients with incident AF were categorized into 3 groups based on the location/setting of the first presentation: outpatient clinic, emergency department, and hospitalization; these groups were mutually exclusive. Given that administrative coding to distinguish between atrial fibrillation and atrial flutter is not reliable,[9] these conditions were combined.

Data sources

Data were acquired by linking 6 population databases maintained by the Alberta Ministry of Health as reported previously.[10] These consist of the following: (i) the Ambulatory Care database, which tracks all visits to the 101 emergency departments (EDs) in Alberta; (ii) the Discharge Abstract Database, which records all admissions to acute care facilities; (iii) the Physician Claims Database, which tracks all fee-for-service claims for insured health services; (iv) the Alberta Population Registry and Alberta Vital Statistics, which track vital statistics for Alberta inhabitants; and (v) the Pharmacy Information Network, which provides all prescriptions filled in Alberta from 2008 onward. Thus, only patients diagnosed in the 2008-2014 fiscal years were included in the prescription analysis. Medications were classified using the *2016 Guidelines for Anatomical Therapeutic Chemical Classification and Defined Daily Dose Assignment*, 9th Edition.[11] The *Canadian Classification of Health Interventions* (CCI), volume 3, was used for procedural interventions,[12] which included 1.HH.59 and 1.HZ.59 (cardiac ablation) and 1.HZ.09 (electrical cardioversion; Supplemental Table S1).

Definitions

Unexplained AF was diagnosed when incident AF occurred in the absence of (i) chronic predisposing comorbidities 3 years before and 1 year after the index AF diagnosis and (ii) predisposing acute events present 1 month before and 1 month after the index AF diagnosis. In selecting these periods for detecting chronic comorbidities, we intended to balance the importance of identifying relevant diagnoses with the historical availability of data in the linked administrative datasets. A 1-year period following AF diagnosis was selected to allow for standard outpatient follow-up and risk-factor assessment to occur after any ED presentation with AF. These AF-predisposing comorbid and acute conditions were identified using ICD9 and ICD10 codes from inpatient, ambulatory, and physician office databases and are listed

comprehensively in Supplemental Tables S2 and S3. In brief, chronic AF-predisposing comorbidities included any diagnosis of thyroid disorder, circulatory system disease (including congenital heart disease), lung disease, diabetes, malignancy, and/or obesity. Acute AF-predisposing events included infections, major trauma, poisonings/overdoses and/or major surgeries. Surgical procedures were identified using CCI, volume 3; a surgery requiring overnight hospitalization was defined as an acute AF-predisposing event. If any of these aforementioned factors were present within the pre-specified time periods, the case was classified as "secondary AF," with all the remaining cases considered to be unexplained AF. Patients were further subdivided by age ($\leq$ 65 years or $>$ 65 years) at the time of diagnosis, to define younger and older AF onset, respectively. We used a cutoff of 65 years to define young onset of AF because this was similar to that used in recent studies[5,6] and reflects the age at which oral anticoagulants (OACs) would be started in Canada, regardless of other stroke risk factors.[7]

Outcomes

The primary outcome of interest was a composite of stroke, transient ischemic attack (TIA), systemic thromboembolism, or death at 1 and 3 years of follow-up. Other endpoints examined were AF repeat healthcare encounters in the hospital or ED (as a primary diagnosis) and re-presentation/hospitalization for noncardiovascular causes at 1 and 3years. We also examined the impact of sex and age on unexplained AF diagnosis and outcomes. Death was considered to be a competing risk during follow-up for repeat AF healthcare encounters.

Statistical analysis

Categorical variables are presented as frequencies with percentages and are compared across groups, using χ^2 tests. Annual household income and age were presented as median with interquartile range (25th, 75th percentiles) and compared across groups using the Mann-Whitney U test. We examined baseline characteristics, outcomes, and medication uptake among young AF patients, stratified by unexplained AF and secondary AF, and among unexplained AF patients, stratified by age group (young: $\leq$ 65 years vs old: $>$ 65 years) and sex (male vs female). We also calculated the incidence of AF indexed to the Alberta population by fiscal year overall, stratified by type of AF (unexplained vs secondary), and by age group (young vs old). To examine the temporal trend in the incidence, we applied Poisson regression models or negative binomial models in case of over dispersion, as appropriate.

In addition, we examined medication uptake and outcomes at 3 years from the diagnosis of AF, specifically examining the trends based on age and type of AF. For this analysis, we excluded patients who were diagnosed with incident AF after March 31, 2012, to provide the same opportunity for 3-year follow up for each patient. Cumulative incidences for primary endpoint and for recurrent AF at 3 years were plotted using Kaplan-Meier curves. Composite outcome at 3 years was compared by type of AF, age group (young vs old), and sex, using Cox's proportional hazard regression model. We also compared use of evidence-based medication including OAC, rate-control medication, by AF type, as well as by age and sex, among young patients with unexplained AF.[7] For all analyses, statistical significance was defined as a 2-sided P value of < 0.05. Analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC). No correction for multiple testing was performed, because the study was exploratory in nature.

Results

AF diagnosis and incidence in the entire cohort

Of 53,059 patients with AF, 33,150 (62.5%) received a new diagnosis of AF during the study period, 1145 (3.5%) of whom had unexplained AF. We subdivided this latter group further by age $>$ 65 years (214; 18.7% of unexplained AF) vs $\leq$ 65 years (931; 81.3% of unexplained AF) at diagnosis, to reflect the point in life at which AF may be related primarily to aging, and which is the indication for anticoagulation in Canada, regardless of other secondary risk factors. Supplemental Figure S1 summarizes the study population grouped by age and AF type. The incidence rate of all-cause AF (unexplained and secondary) rose steadily, on average by 1.7% per year, over the study period (rate ratio 1.017; 95% confidence interval [CI]: 1.012-1.22); $P < 0.001$; Fig. 1).

Diagnosis and outcomes of AF regardless of age

We first compared unexplained AF to secondary AF, regardless of age at diagnosis (Table 1). Over the study period, the incidence of both unexplained AF and secondary AF increased (4.1%, $P = 0.003$; 1.6%; $P < 0.001$, respectively, Fig. 1). As anticipated, at 1 and 3 years, there was a greater risk of all adverse endpoints in secondary AF compared to unexplained AF (Fig. 2; Table 2). In unexplained AF, electrical cardioversion was attempted more frequently, compared with its use for secondary AF patients (24.4% vs 12.7% at 30 days; $P < 0.001$), whereas secondary AF patients were more likely to undergo catheter ablation, compared with patients with unexplained AF (1.7% vs 0.3% at 1 year; $P < 0.001$; Table 2).

Diagnosis and outcomes of AF in the young

We then focused on younger patients with AF (aged $\leq$ 65 years at diagnosis; Table 3). Age of onset in unexplained AF in the young (42 years, interquartile range [IQR] 32-53) was lower, compared with that for secondary AF in the young (55 years, IQR 47-61; $P < 0.001$). The incidence of AF in the young rose on average by 2.1% per year over the study period ($P < 0.001$), including increases in both unexplained (3.8% per year) and secondary AF (2.2% per year; Fig. 3). In the young population, the location of diagnosis also differed, with secondary AF more likely to be diagnosed in outpatient and inpatient settings, and unexplained AF more likely to be diagnosed in the ED; Table 3). At 1 and 3years, a higher proportion of secondary AF patients, compared with patients with unexplained AF, experienced all adverse endpoints (Table 4; Fig. 4). Important to note is that in young-onset unexplained AF, the risk of the primary outcome was low (at 1 year, 6 patients [0.6%]; at 3 years, 10 patients [1.7%]). This finding contrasts with results for those with young-onset secondary AF, which was associated with a risk of the primary

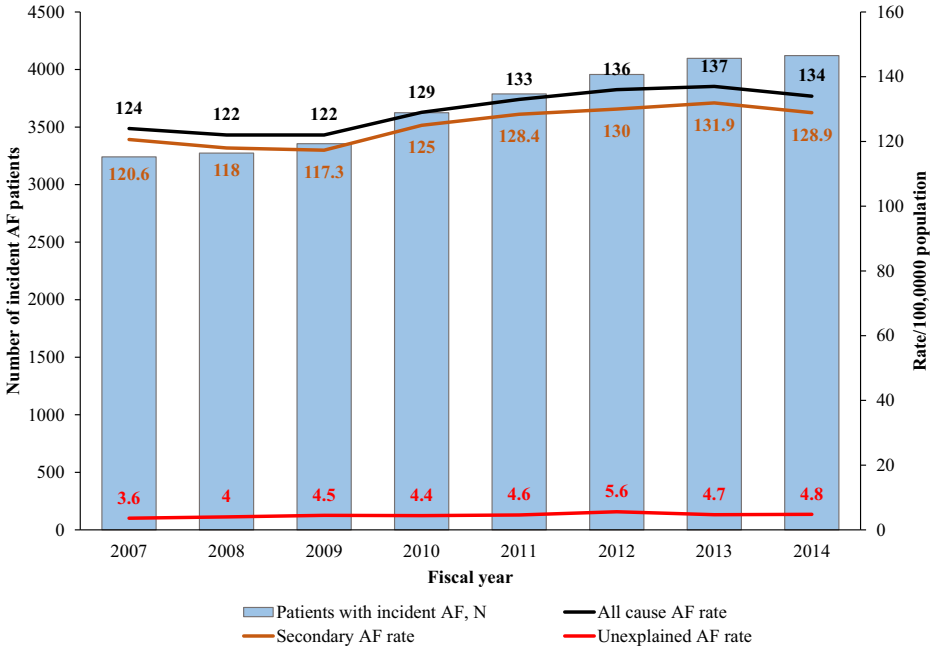

Figure 1. Incidence rate of all-cause (unexplained and secondary) atrial fibrillation and atrial flutter (AF) indexed to 100,000 of the Alberta population.

outcome of 4.0% at 1 year and 8.0% at 3 years. Trends in hospital utilization during follow-up in patients aged ≤ 65 years are shown in Table 4.

Management strategies were then studied in this younger age group. Specifically, we evaluated the prescription and procedural utilization trends, but we did not undertake

Table 1. Characteristics of new-onset atrial fibrillation and atrial flutter (AF) patients—unexplained vs secondary

Characteristics	Unexplained AF	Secondary AF	Total	*P*
n	1145	32,005	33,150	
Age at presentation, y	47 (35, 61)	72 (61, 80)	71 (60, 80)	< 0.0001
Age group, y				
20–44	512 (44.7)	2097 (6.6)	2609 (7.9)	< 0.0001
45–54	216 (18.9)	2759 (8.6)	2975 (9.0)	
55–65	203 (17.7)	5422 (16.9)	5625 (17.0)	
66–79	154 (13.4)	12,896 (40.3)	13,050 (39.4)	
≥ 80	60 (5.2)	8831 (27.6)	8891 (26.8)	
Sex (male)	852 (74.4)	16,970 (53.0)	17,822 (53.8)	< 0.0001
Chronic comorbid diagnoses				
Malignancy	0 (0)	11,399 (35.6)	11,399 (34.4)	
Thyroid disease	0 (0)	6032 (18.8)	6032 (18.2)	
Cardiovascular and cerebrovascular disease	0 (0)	30,247 (94.5)	30,247 (91.2)	
Chronic lung disease	0 (0)	11,090 (34.7)	11,091 (33.5)	
Diabetes	0 (0)	8258 (25.8)	8258 (24.9)	
Obesity and metabolic disorders	0 (0)	17,255 (53.9)	17,255 (52.1)	
Acute comorbid events/diagnoses				
Selected injuries and poisonings	0 (0)	1222 (3.8)	1224 (3.7)	
Burns	0 (0)	26 (0.1)	26 (0.1)	
Acute respiratory infection	0 (0)	1719 (5.4)	1744 (5.3)	
Pneumonia and influenza	0 (0)	1889 (5.9)	1892 (5.7)	
Appendicitis	0 (0)	20 (0.1)	20 (0.1)	
Other infections	0 (0)	2802 (8.8)	2811 (8.5)	
Locale of diagnosis				
Specialist's outpatient clinic	223 (19.5)	9373 (29.3)	9596 (28.9)	< 0.0001
Emergency department	803 (70.1)	15,352 (48.0)	16,155 (48.7)	
Inpatient	119 (10.4)	7280 (22.7)	7399 (22.3)	
Residence				
Rural	207 (18.1)	6060 (18.9)	6267 (18.9)	0.4673
Urban	938 (81.9)	25,945 (81.1)	26,883 (81.1)	
Median household total income in 2010, $	75,143 (67,856, 94,410)	73,385 (66,341, 90,652)	73,385 (66,341, 90,652)	0.0022

Values are n (%) or median (interquartile range), unless otherwise indicated.

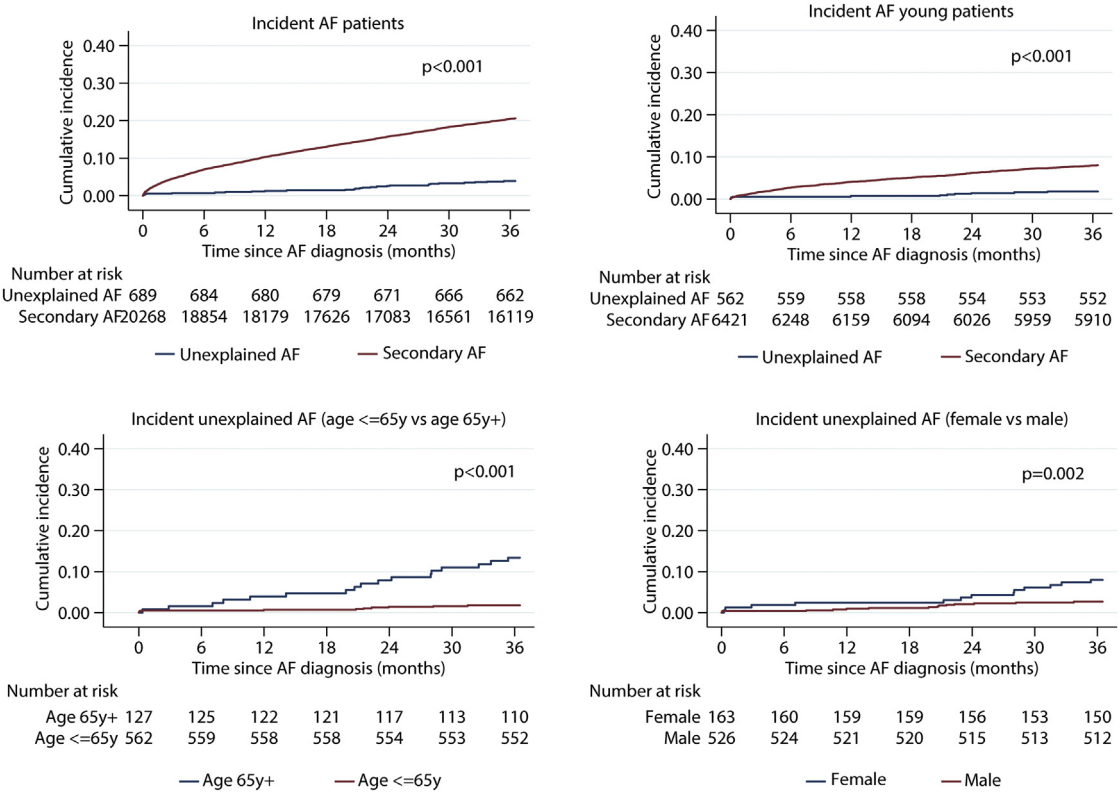

Figure 2. Cumulative incidence composite outcomes (death/stroke/transient ischemic attack/embolism) at 3 years since the diagnosis of atrial fibrillation and atrial flutter (AF).

analyses examining the interaction between outcome and therapy, owing to the large number of confounding factors that could not be accurately adjusted for in the cohort.

Tables 2 and 4 summarize catheter ablation and electrical cardioversion interventions at 1 year. In both the older and younger populations, electrical cardioversion was more

Table 2. Treatments and outcomes of new-onset atrial fibrillation and atrial flutter (AF)—unexplained vs secondary

Variable	Unexplained AF	Secondary AF	Total	*P*
n	1145	32,005	33,150	
Catheter ablation				
7-d	1 (0.1)	94 (0.3)	95 (0.3)	0.1993
30-d	1 (0.1)	135 (0.4)	136 (0.4)	0.0819
1-y	3 (0.3)	533 (1.7)	536 (1.6)	0.0002
Electrical cardioversion				
7-d	273 (23.8)	3812 (11.9)	4085 (12.3)	< 0.0001
30-d	282 (24.6)	4069 (12.7)	4351 (13.1)	< 0.0001
1-y	312 (27.2)	5667 (17.7)	5979 (18.0)	< 0.0001
1-y outcome				
Deaths	12 (1.0)	2640 (8.2)	2652 (8.0)	< 0.0001
Stroke	2 (0.2)	539 (1.7)	541 (1.6)	< 0.0001
Stroke/TIA/embolism	4 (0.3)	806 (2.5)	810 (2.4)	< 0.0001
Death/stroke/TIA/embolism	16 (1.4)	3262 (10.2)	3278 (9.9)	< 0.0001
Bleeding	3 (0.3)	1525 (4.8)	1528 (4.6)	< 0.0001
Hospitalization/ED visit for AF	187 (16.3)	6762 (21.1)	6949 (21.0)	< 0.0001
Non-CV hospitalization/ED visit	362 (31.6)	16,812	17,174 (51.8)	< 0.0001
3-y outcome				
n	689	20,286	20,975	
Deaths	20 (2.9)	3415 (16.8)	3435 (16.4)	< 0.0001
Stroke	6 (0.9)	793 (3.9)	799 (3.8)	< 0.0001
Stroke/TIA/embolism/death	27 (3.9)	4205 (20.7)	4232 (20.2)	< 0.0001
Bleeding	20 (2.9)	1993 (9.8)	2013 (9.6)	< 0.0001
Hospitalization/ED visit for AF	169 (24.5)	5920 (29.2)	6089 (29.0)	0.0081
Non-CV hospitalization/ED visit	378 (54.9)	15,013 (74.0)	15,391 (73.4)	< 0.0001

Values are n (%), unless otherwise indicated.
CV, cardiovascular; ED, emergency department; TIA, transient ischemic attack.

Table 3. Comparisons of characteristics among young (age ≤ 65 years) patients—unexplained vs secondary atrial fibrillation and atrial flutter (AF)

Characteristics	Unexplained AF	Secondary AF	Total	*P*
n	931	10,278	11,209	
Age at presentation	42 (32, 53)	55 (47, 61)	55 (45, 60)	< 0.0001
Age group, y				
20–44	512 (55.0)	2097 (20.4)	2609 (23.3)	< 0.0001
45–54	216 (23.2)	2759 (26.8)	2975 (26.5)	
55–65	203 (21.8)	5422 (52.8)	5625 (50.2)	
Sex (male)	735 (78.9)	6637 (64.6)	7372 (65.8)	< 0.0001
Locale of diagnosis				
Specialist's outpatient clinic	160 (17.2)	2805 (27.3)	2965 (26.5)	< 0.0001
Emergency department	673 (72.3)	5448 (53.0)	6121 (54.6)	
Inpatient	98 (10.5)	2025 (19.7)	2123 (18.9)	
Residence				
Rural	165 (17.7)	1871 (18.2)	2036 (18.2)	0.7154
Urban	766 (82.3)	8407 (81.8)	9173 (81.8)	
Median household total income in 2010, $	75,684 (68,090, 96,257)	75,857 (68,090, 94,410)	75,857 (68,090, 94,410)	0.8748

Values are n (%) or median (interquartile range), unless otherwise indicated.

commonly used for unexplained AF, whereas ablation was more commonly used for secondary AF. Specifically, 3 patients with unexplained AF (0.3%) underwent ablation within 1 year, vs 533 patients with secondary AF (1.7%; $P < 0.001$). Electrical cardioversion by 1 year occurred in 27.7% with unexplained AF vs 17.7% with secondary AF ($P < 0.001$). A rate-control strategy using atrioventricular nodal blockers was attempted in a small number of young patients with unexplained AF (Supplemental Tables S4-S6), with most beta-blocker prescriptions occurring in the first 30 days after diagnosis (166 of 223 patients; 74.4%). In young-onset secondary AF, beta-blockers were used in 37.7% at 30 days (3234 patients) and in 56.3% by 1 year (4836 patients) after diagnosis. All types of rate-control drugs were prescribed more often in secondary AF than in unexplained AF at 30 days and 1 year ($P < 0.001$) after diagnosis. Patients with unexplained AF were less likely to receive an anti-arrhythmic drug at all follow-up points examined ($P < 0.001$). Supplemental Table S4 summarizes OAC prescriptions in the young.

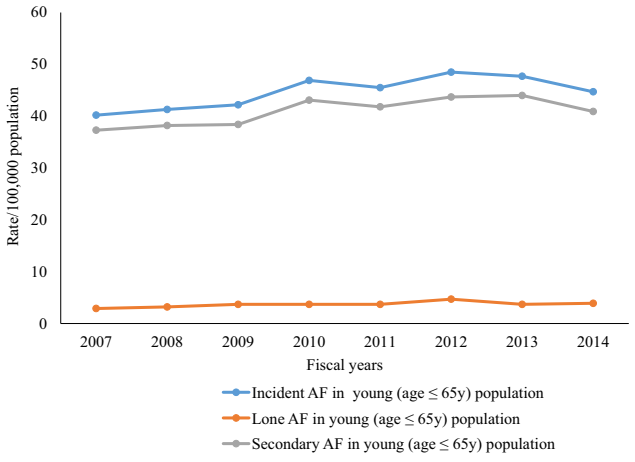

Figure 3. Incidence rate of atrial fibrillation and atrial flutter (AF) among the young (age ≤ 65 years) population.

Sex- and age-based trends by AF type, diagnosis, and outcomes

We next assessed for sex- and age-based trends (Table 5; Supplemental Table S7). Women with unexplained AF were older (58 [IQR 40-69] vs 45 [IQR 34-59] years; $P < 0.001$), were more often diagnosed as outpatients (28% vs 17%; $P < 0.001$), and were more likely to experience the primary composite endpoint at 1 and 3 years, compared with men (2.7% vs 0.9%; $P = 0.024$ and 7.8% vs 2.6%; $P = 0.002$, respectively). However, after adjusting for age at diagnosis, women and men had similar outcomes (Fig. 4). There were also no significant differences based on sex for OAC prescription at 1 year (Supplemental Table S8). Women were more likely to receive calcium-channel blockers (10.8 vs 6.3%; $P = 0.018$) and digoxin (2.8 vs 0.7%; $P = 0.009$) in the first year after diagnosis. A higher proportion of men underwent electrical cardioversion, compared with women (31.2% vs 15.7% at 1year; $P < 0.001$). Hospitalization/ED visit for AF after index diagnosis were greater at 1 year in men vs women (17.7% vs 12.3%; $P = 0.029$), including among young patients with unexplained AF (18.2% vs 11.1%; $P = 0.018$). Age also predicted diagnosis and outcomes (Table 5; Fig. 4). When combining both AF classifications, those in the earlier-onset group (age ≤ 65 years) were more likely to be male (78.9 vs 54.7%; $P < 0.001$) and to be diagnosed in the emergency/inpatient setting than women. For unexplained AF, older-onset patients were more likely to suffer from the primary composite outcome than younger patients at 1 year (4.7 vs 0.6%; $P < 0.001$) and 3 years (13.2 vs 1.7%, $P < 0.001$). There were no significant differences in AF or non-cardiovascular disease hospitalization/ED visit by age in follow-up (Table 5). As expected, OAC (38.0 vs 14.0%; $P < 0.001$), beta-blocker (37.4 vs 28.3%; $P = 0.017$), and calcium-channel blocker (15.1 vs 5.7%; $P < 0.001$) prescription occurred more in older patients with unexplained AF at 1 year than in younger AF patients (Supplemental Table S6).

Discussion

This population study demonstrates that unexplained AF, defined using stringent contemporary criteria, has a lower than

Table 4. Cardiac intervention and outcomes among young (age ≤ 65 years) patients with unexplained vs secondary atrial fibrillation and atrial flutter (AF)

Variable	Unexplained AF	Secondary AF	Total	*P*
n	931	10,278	11,209	
Catheter ablation				
7-d	0 (0.0)	50 (0.5)	50 (0.4)	0.0329
30-d	0 (0.0)	74 (0.7)	74 (0.7)	0.0094
1-y	2 (0.2)	298 (2.9)	300 (2.7)	< 0.0001
Electrical cardioversion				
7-d	250 (26.9)	1873 (18.2)	2123 (18.9)	< 0.0001
30-d	257 (27.6)	1977 (19.2)	2234 (19.9)	< 0.0001
1-y	283 (30.4)	2693 (26.2)	2976 (26.6)	0.0055
1-y outcome				
Death	5 (0.5)	309 (3.0)	314 (2.8)	< 0.0001
Stroke	1 (0.1)	79 (0.8)	80 (0.7)	0.0217
Death/stroke/TIA/embolism	6 (0.6)	410 (4.0)	416 (3.7)	< 0.0001
Bleeding	2 (0.2)	283 (2.8)	285 (2.5)	< 0.0001
Hospitalization/ED visit for AF	156 (16.8)	2325 (22.6)	2481 (22.1)	< 0.0001
Non-CV hospitalization/ED visit	305 (32.8)	4855 (47.3)	5160 (46.0)	< 0.001
3-y outcome				
n	562	6424	6986	
Death	8 (1.4)	378 (5.9)	386 (5.5)	< 0.0001
Stroke	0 (0.0)	119 (1.9)	119 (1.7)	0.0011
Stroke/TIA/embolism/death	10 (1.8)	524 (8.2)	534 (7.6)	< 0.0001
Bleeding	16 (2.8)	364 (5.7)	380 (5.4)	0.0047
Hospitalization/ED visit for AF	134 (23.8)	2001 (31.1)	2135 (30.6)	0.0003
Non-CV hospitalization/ED visit	314 (55.9)	4381 (68.2)	4695 (67.2)	< 0.0001

Values are n (%), unless otherwise indicated.

CV, cardiovascular; ED, emergency department; TIA, transient ischemic attack.

previously reported incidence and carries a small risk of serious complications during short- and medium-term follow-up. However, acute hospital encounters for AF and non-cardiovascular diagnoses frequently follow the unexplained AF diagnosis. Important sex-based differences exist, highlighted by a disproportionately young age at onset in men, who carry a higher chance of AF re-presenting during follow-up. However, no sex-based differences for the primary outcome existed after adjusting for age. Collectively, these data suggest that unexplained AF is less common than previously reported, and it has unique demographic characteristics and outcomes that warrant further study.

In keeping with established trends in all-cause AF, the impact of male sex on unexplained AF susceptibility was pronounced in our study, with a 13-year lower median age of disease onset. Although previous studies have not clearly identified biological explanations for sex differences, elevated bioavailable testosterone appeared to increase AF risk in the

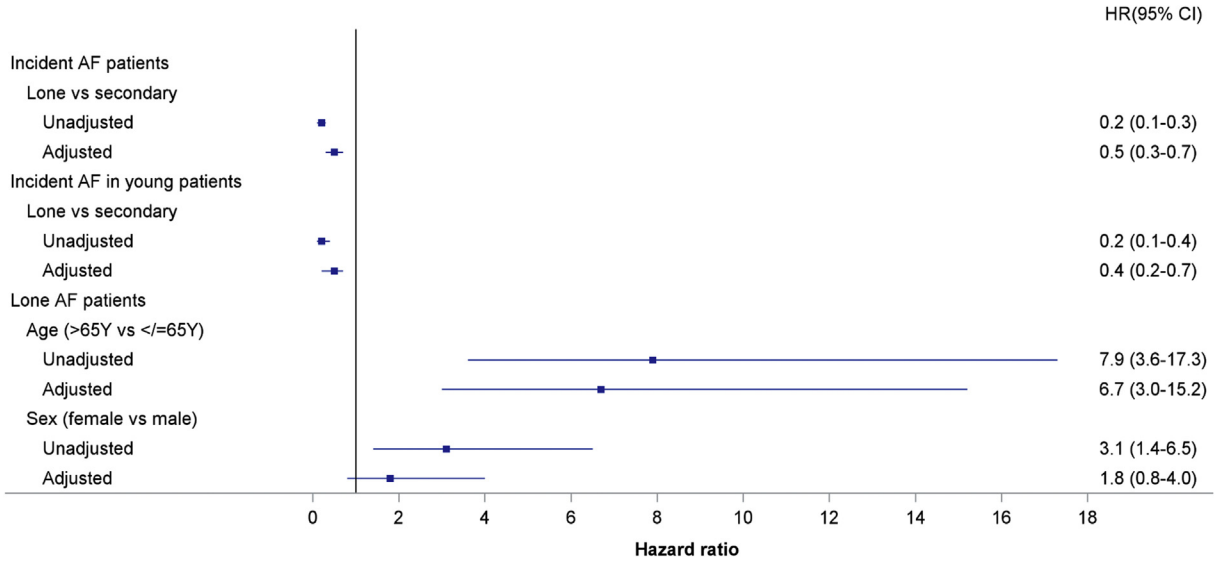

Figure 4. Hazards of composite outcome (death/stroke/transient ischemic attack/embolism) at 3 years; hazards are adjusted for age and sex. AF, atrial fibrillation and atrial flutter; CI, confidence interval; HR, hazard ratio.

Table 5. Characteristics of patients with unexplained atrial fibrillation and atrial flutter (AF) patients, stratified by age (young vs old) and by sex (women vs men)

Variable	Age ≤ 65 y	Age > 65 y	*P*	Women, all ages	Men, all ages	*P*
n	931	214		293	852	
Age,y	42 (32, 53)	73 (68, 81)	< 0.001	58 (40, 69)	45 (34, 57)	< 0.001
Sex (male)	735 (78.9)	117 (54.7)	< 0.001	—	—	
Locale of diagnosis						
Specialist's outpatient clinic	160 (17.2)	63 (29.4)	< 0.001	81 (27.6)	142 (16.7)	< 0.001
ED	673 (72.3)	130 (60.7)		184 (62.8)	619 (72.7)	
Inpatient	98 (10.5)	21 (9.8)		28 (9.6)	91 (10.7)	
Residence						
Rural	165 (17.7)	42 (19.6)	0.51	51 (17.4)	156 (18.3)	0.73
Urban	766 (82.3)	172 (80.4)		242 (82.6)	696 (81.7)	
Neighborhood household income in 2010, $	75,684 (68,090, 96,257)	72,369 (64,996, 90,935)	0.05	73,590 (65269, 94,410)	75,406 (68,090, 96,257)	0.16
Electrical cardioversion						
7-d	250 (26.9)	23 (10.7)	< 0.001	42 (14.3)	231 (27.1)	< 0.001
30-d	257 (27.6)	25 (11.7)	< 0.001	44 (15.0)	238 (27.9)	< 0.001
1-y	283 (30.4)	29 (13.6)	< 0.001	46 (15.7)	266 (31.2)	< 0.001
1-y outcome						
Death	5 (0.5)	7 (3.3)	< 0.001	5 (1.7)	7 (0.8)	0.20
Stroke	1 (0.1)	1 (0.5)	0.26	1 (0.3)	1 (0.1)	0.43
Death/stroke/TIA/embolism	6 (0.6)	10 (4.7)	< 0.001	8 (2.7)	8 (0.9)	0.024
Bleeding	2 (0.2)	1 (0.5)	0.52	1 (0.3)	2 (0.2)	0.76
Hospitalization/ED visit for AF	156 (16.8)	31 (14.5)	0.42	36 (12.3)	151 (17.7)	0.03
Non-CV hospitalization/ED visit	305 (32.8)	57 (26.6)	0.079	95 (32.4)	267 (31.3)	0.73
3-y outcome						
n	572	129		166	535	
Death	8 (1.4)	12 (9.3)	< 0.001	8 (4.8)	12 (2.2)	0.08
Stroke/TIA/embolism/death	10 (1.7)	17 (13.2)	< 0.001	13 (7.8)	14 (2.6)	0.002
Bleeding	16 (2.8)	5 (3.9)	0.52	5 (3.0)	16 (3.0)	0.99
Hospitalization/ED visit for AF	136 (23.8)	35 (27.1)	0.42	30 (18.1)	141 (26.4)	0.029
Non-CV hospitalization/ED visit	324 (56.6)	66 (51.2)	0.26	92 (55.4)	298 (55.7)	0.95

Values are n (%) or median (interquartile range), unless otherwise indicated.
CV, cardiovascular; ED, emergency department; TIA, transient ischemic attack.

Multi-Ethnic Study of Atherosclerosis, and X-linked recessive factors may play a role in kindred AF.[13,14] In our study, we could not rule out lifestyle as an environmental contributor, such as potential sex-based differences in alcohol intake, obesity, exercise, and smoking. Despite observing a preponderance of men with earlier-onset unexplained AF, women were at a similar risk for death, stroke, TIA, and systemic thromboembolism, after adjusting for age at diagnosis. Recent studies on nonvalvular AF have attempted to clarify the controversial role of sex on stroke risk.[15,16] These data show that men and women face a similar risk of stroke, with the exception of elderly women, who are at slightly higher risk.[16] Important to note is that we found no sex-based trends in OAC prescription. However, digoxin and calcium-channel blockers were more often used in women; these are traditionally viewed as second-line rate-control agents. We could not determine whether physician bias or beta-blocker intolerance/refractoriness drove this difference.

The incidence of unexplained and secondary AF rose throughout the study period. This increase may be due to recent increasing awareness and subclinical detection of AF. Another possibility is that metabolic risk factors, such as obesity, were incompletely coded and contributed to this trend. Important to note is that when we applied a more stringent definition to unexplained AF, including young age of onset, the incidence compared to secondary AF was lower (2.8% of all new AF diagnoses) than historical estimates (up to 30% of all AF diagnoses),[6] and was in keeping with recent registry data (3%).[17] This variation is likely due to under-recognized secondary AF triggers and use of inconsistent definitions of unexplained AF over time.[6] Indeed, the very existence of truly unexplained, lone, or idiopathic AF is increasingly being challenged, especially with the advent of complex genetic analysis.[6,18]

The incidence of unexplained AF, and the growing role of genetic testing, has important clinical relevance. Emerging data show that many young patients and their families afflicted by early-onset AF have predisposing Mendelian[6] and complex genetic substrate.[18] In the past few years, truncating variants in the gene encoding Titin have emerged as strong risk factors for unexplained AF, especially in the young.[19,20] Similarly, polygenic risk models suggest that early-onset unexplained AF can be accounted for by the cumulative burden of common susceptibility variants.[18] Future opportunities to detect unexplained early-in-life AF may improve outcomes and lead to tailored therapy.[21] The present study provides an estimate of the number of AF cases that could benefit from further genomic analysis. We argue that the emerging relevance of genetic testing in this field necessitates that unexplained AF be defined more stringently, to illuminate who is most likely to benefit from clinically indicated genetic sequencing, family screening, and eventually precision therapy.

Limitations

This is a population-level study of retrospective administrative data. The amount, frequency, and symptoms of AF

could not be ascertained. We could not adjust for some environmental contributors to AF such as alcohol intake, exercise, diet, and smoking, as they are either poorly coded or not coded at all. Similarly, the ICD codes for comorbidities and procedures were not universally validated; however, AF codes have strong positive and negative predictive value in validation cohorts.[8,9,22] To increase the probability that unexplained AF was truly unexplained/idiopathic, we classified all cases with an identifiable AF-predisposing condition as being secondary AF. However, some of these conditions may not contribute to the pathogenesis of AF. Thus, patients may have been included in the secondary AF group who did not develop AF due to a comorbidity (eg, hypothyroidism or minor infection), meaning that the pathogenesis of AF was unexplained. Unfortunately, it is not possible to determine the precise cause of AF in many clinical circumstances, regardless of study design.

The definition of the maximal age at which unexplained AF can be diagnosed remains ambiguous. Here, we used a cutoff of age 65 years to define young-onset AF, because this was similar to the age used in recent classifications,[5,6] and it reflects the age at which OACs are indicated in Canada, regardless of other stroke risk factors.[7] These challenges related to disease definitions and coding consistency are inherent to all administrative population datasets, and the trends described here are hypothesis-generating. The data may be most useful to clinicians and researchers needing to understand the approximate number and proportion of AF patients who may benefit from future biological or genetic studies aimed at identifying factors involved in the pathogenesis of unexplained AF.

When conducting event analyses, we adjusted for the 2 covariates most likely to influence outcomes (age and sex), based on existing data. Owing to the small population of patients with unexplained AF and the limited number of patients with composite outcome events at 3 years in this group (27 patients), we could not adjust for additional covariates in our modeling. Death was considered to be a competing risk for repeat AF healthcare encounters (Supplemental Fig. S2). However, for the exploratory outcome of repeat non−AF related hospital encounters, a competing risk model was not constructed because mortality was very low at 3 years in the unexplained AF group (1.7%), and death as a competing risk did not significantly influence the primary outcome or repeat AF encounter outcome. The secondary AF group may have shown a higher probability of being rehospitalized for a non-AF diagnosis, had a competing risk model been developed. However, secondary AF was not the focus of the present study.

Conclusions

The incidence of unexplained AF is lower than that previously reported when a stringent contemporary definition of the condition is applied. Unexplained AF is a predominantly male disorder complicated by a high rate of recurrent hospital utilization but low rates of stroke, TIA, systemic thromboembolism, and death over 3 years of follow-up. Additional studies are needed to provide an explanation for AF in these individuals, and to identify factors that lead to recurrent hospitalization.

Funding Sources

The Canadian Arrhythmia Network (CANet) and the University Hospital Foundation supported this study. T.M.R. is funded by the University of British Columbia Clinician Investigator Program, and is a Friedman Scholar in Health and a George Mines Traveling Fellow in Cardiac Electrophysiology. A.D.K. receives support from the Sauder Family and Heart and Stroke Foundation Chair in Cardiology (Vancouver, British Columbia), the Paul Brunes Chair in Heart Rhythm Disorders (Vancouver, British Columbia), and the Paul Albrechsten Foundation (Winnipeg, Manitoba). Z.L. received support from the Michael Smith Foundation for Health Research and the Cardiology Academic Partnership Plan, University of British Columbia.

Disclosures

The authors have no conflicts of interest to disclose. This study is based in part on data provided by Alberta Health. The interpretation and conclusions contained herein are those of the researchers and do not necessarily represent the views of the Government of Alberta. Neither the Government of Alberta nor Alberta Health expresses any opinion in relation to this study.

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Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at https://www.cjcopen.ca/ and at https://doi.org/10.1016/j.cjco.2021.09.006.