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ORIGINAL RESEARCH

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Outcomes Associated With Familial Versus Nonfamilial Atrial Fibrillation: A Matched Nationwide Cohort Study

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***Background*—**We examined all-cause mortality and long-term thromboembolic risk (ischemic stroke, transient ischemic attack, systemic thromboembolism) in patients with and without familial atrial fibrillation (AF).

***Methods and Results*—**Using Danish nationwide registry data, we identified all patients diagnosed with AF (1995–2012) and divided them into those with familial AF (having a first-degree family member with a prior AF admission) and those with nonfamilial AF. We paired those with and without familial AF according to age, year of AF diagnosis, and sex in a 1:1 match. Using cumulative incidence and multivariable Cox models, we examined the risk of long-term outcomes. We identified 8658 AF patients (4329 matched pairs) with and without familial AF. The median age was 50 years (interquartile range 43–54 years), and 21.4% were women. Compared with nonfamilial AF patients, those with familial AF had slightly less comorbid illness but similar overall CHA_2DS_2-VASc score (P=0.155). Median follow-up was 3.4 years (interquartile range 1.5–6.5 years). Patients with familial AF had risk of death and thromboembolism similar to those with nonfamilial AF (adjusted hazard ratio 0.91 [95% CI 0.79–1.04] for death and 0.90 [95% CI 0.71–1.14] for thromboembolism).

***Conclusions*—**Although family history of AF is associated with increased likelihood for development of AF, once AF developed, long-term risks of death and thromboembolic complications were similar in familial and nonfamilial AF patients. **(*J Am Heart Assoc*. 2016;5:e003836 doi: 10.1161/JAHA.116.003836)**

Key Words: atrial flutter • complication • family history • genetics

A complete understanding of atrial fibrillation (AF) and its pathophysiology is lacking. Since 1997, several single-point genetic loci have been correlated to AF,[1–5] suggesting a genetic etiology for AF, at least in some cases. Three specific genomic regions associated with AF were identified recently through genomewide association studies of chromosome 4q25, 16q22, and 1q21.[6–9] In addition, recent studies showed that AF aggregates in families.[10–15] These studies indicated that family history of AF may be considered an important risk factor for AF. Furthermore, patients with first-degree relatives diagnosed with AF (familial AF) have been shown to be younger and to have less comorbidity than AF patients without a family history of AF.[10–12,16,17] Nevertheless, no long-term outcome data exist for familial AF.

Death and thromboembolism are important long-term complications of AF; for example, AF is associated with a 5-fold increased risk of stroke.[18] Antithrombotic treatment is used to prevent thromboembolic complications in these patients, and the treatment strategy is independent of family history of AF. Information regarding potential differences in these outcomes among familial and nonfamilial AF patients is needed to help clarify whether these 2 patient groups would benefit from different treatment strategies.

The aim of this study was to examine all-cause mortality and thromboembolic risk (stroke, transient ischemic attack, systemic thromboembolism) in AF patients with familial AF compared with patients with nonfamilial AF.

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Accompanying Tables S1 and S2 are available at http://jaha.ahajournals.org/content/5/11/e003836/DC1/embed/inline-supplementary-material-1.pdf

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Methods

Data Sources

All residents of Denmark are included in a set of nationwide administrative registries. The Danish Civil Registration System (since 1968) holds complete information about sex and date of birth.[19] It includes complete information about parents (at least the mother) from 1930 onward and about siblings from 1942 onward. All in- and outpatient hospital contacts (not including general practitioner visits) in Denmark are registered in the Danish National Patient Registry (since 1978), in which all given diagnoses at discharge are registered in terms of International Classification of Diseases (ICD) codes. In Denmark, the eighth revision (ICD-8) was used until 1994, and the 10th revision (ICD-10) was used thereafter.[20] All dispensed prescriptions have been registered since 1995 at an individual level in the Danish National Registry of Medicinal Statistics. The registry is complete because all Danish pharmacies are mandated by law to register and report all filled prescriptions.[21] It is also mandatory under Danish law for physicians to complete a death certificate for any death occurring in Denmark. This certificate is registered in the Danish Register of Causes of Death, which holds information about the cause of death.[22] For the purpose of this study, we linked data from these 4 registries using personal identification numbers that all residents of Denmark are given at birth or immigration.

Study Patients

We included all Danish residents born after January 1, 1895, who were diagnosed with AF in the period from 1995 to 2012. Adopted and stillborn persons were excluded. First, we identified all AF patients who had a proband diagnosed with AF and defined these patients as the familial AF patients that constituted the cases in the study. A proband was defined as a first-degree family member (parent or sibling) who was diagnosed with AF in the period 1978 to 2012 and prior to the date of the AF diagnosis of the case. Siblings were defined as 2 persons having the same mother. Second, we identified all AF patients without a proband with AF (controls). We excluded all controls without registration of both parents. We matched the cases and the controls with a 1:1 match for age at AF diagnosis, year of AF diagnosis, and sex, using the Greedy Match method (http://www.mayo.edu/research/documents/gmatchsas/doc-10027248). Patient selection is shown in Figure 1.

The diagnosis of AF was obtained from the Danish National Patient Registry and was defined as a combined diagnosis of AF and atrial flutter (ICD-8 codes 4279 and 42793 and ICD-10 code I48). This diagnosis was validated in a Danish registry-based study with a positive predictive value of 92.6% (95% CI 88.8–95.2%) and no significant difference between sexes (positive predictive value 2.8%, 95% CI −3.4% to 9.0%).[23]

Outcomes

Information about time of death was obtained from the Danish Civil Registration System. A thromboembolic event was defined as stroke (ICD-10 codes I63 and I64), transient ischemic attack (ICD-10 codes G45.8 and G45.9), or systemic embolism (ICD-10 code I74), and data were obtained from the Danish National Patient Registry and the Danish Register of

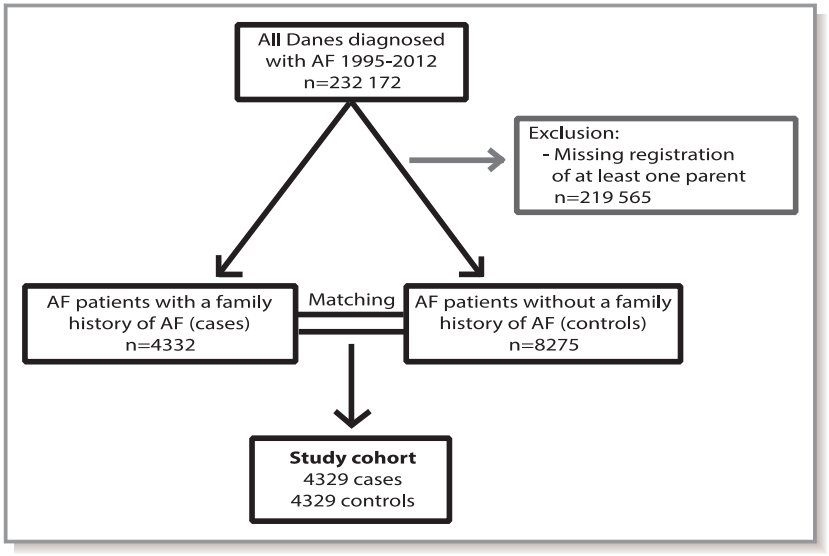

Figure 1. Patient selection. AF indicates atrial fibrillation.

Causes of Death. Patients were followed from the date of their AF diagnosis until the time of event, emigration, death, or the end of study period (December 31, 2012), whichever came first. The accumulation of risk-time began at the date of AF diagnosis.

Statistics

Baseline characteristics including patient demographics, comorbidities, use of pharmacotherapy (in a period from 3 months before the diagnosis of AF until 7 days after discharge), and CHA_2DS_2-VASc score are presented by family history of AF. Characteristics were compared using the Kruskal–Wallis test for continuous variables and the chi-square test for categorical variables. The CHA_2DS_2-VASc score was calculated, as described previously.[24] Using the Kaplan–Meier estimator, we calculated the survival probability according to family history of AF. The cumulative incidence of a thromboembolic outcome in the 2 groups of patients was assessed using the Aalen-Johansen estimator (incorporating the competing risk of death). We tested for differences between the 2 groups using the Fine and Gray test. We estimated the association of a family history of AF with each outcome using multivariable adjusted Cox proportional hazards models. We adjusted for age at AF diagnosis, year of AF diagnosis, sex, comorbidities (including dementia; AIDS; stroke, transient ischemic attack, or systemic embolism; diabetes mellitus; heart valve disease; vascular disease; liver disease; thyroid disease; ischemic heart disease; nonischemic dilated cardiomyopathy; renal disease; hemi- or paraplegia; peptic ulcer; congenital anomalies of the heart; chronic obstructive pulmonary disease; rheumatic disease; cancer; prior shock or sepsis; arrhythmia; heart failure; alcohol abuse; and hypertension), and concomitant pharmacotherapy including nonsteroidal anti-inflammatory drugs, digoxin, corticosteroids, thyroid medication, statins, vitamin K antagonists, antithrombotic medication, non–vitamin K antagonists, class IC antiarrhythmic drugs, class III antiarrhythmic drugs, and verapamil. Tables S1 and S2 specify comorbidities and pharmacotherapy. Finally, we tested for interactions of death and thromboembolic events with ischemic heart disease, peripheral vascular disease, and diabetes mellitus. All model assumptions were tested and found to be valid unless otherwise indicated. A P value <0.05 was considered statistically significant. All statistical analyses were performed in SAS statistical software version 9.4 (SAS Institute) and RStudio (Foundation for Open Access Statistics).

Premature Familial AF

As a selected sensitivity analysis, we restricted the group of familial AF patients to those with a first-degree family member diagnosed with AF before age 70 years. We matched those patients with nonfamilial AF patients based on age at AF diagnosis, year of AF diagnosis, and sex and compared the 2 groups regarding their risk of stroke and all-cause mortality.

Ethics

Approval from the Research Ethics Committee System is not required for retrospective registry-based studies in Denmark. The Danish Data Protection Agency approved use of the data for this study (reference number: 2007-58-0015/GEH-2014-013 I-Suite number: 02731).

Results

We identified a total of 232 172 AF patients diagnosed with AF in Denmark in the period from 1995 to 2012. Of those patients, 4332 had at least 1 AF proband. The cases were matched with the same number of controls, leaving 3 familial AF patients without a suitable match (Figure 1). Table 1 shows the baseline demographics and comorbidities of patients with and without family history of AF. The median age of familial and nonfamilial AF patients was 50 years (interquartile range [IQR] 43–54 years). In the entire Danish AF population diagnosed during 1995 to 2012, the median age at AF diagnosis was 77 years (IQR 67–84 years). In the entire AF population, 47% were women, whereas only 21.4% of the familial AF patients were women. In general, the matched nonfamilial AF patients had more comorbid illness, including ischemic heart disease, vascular disease, diabetes mellitus, alcohol abuse, peptic ulcer, and prior hospital admission for shock and sepsis. For other comorbidities, the 2 groups of patients were comparable. No significant difference in CHA_2DS_2VASc scores existed between the 2 groups of patients (median CHA_2DS_2VASc score 0 [IQR 0–1] for both patient groups, P=0.155).

Table 2 shows the use of pharmacotherapy at baseline. Patients with nonfamilial AF received significantly more treatment for comorbidities (including antiplatelets and statins), whereas more patients with familial AF received vitamin K antagonists and verapamil.

Outcomes

The median follow-up time from AF diagnosis was 3.4 years (IQR 1.5–6.5 years) for familial AF patients and 3.3 years (IQR 3.3–6.4 years) for nonfamilial AF patients. After the first year since AF diagnosis, 4.8% of the familial AF patients and 5.4% of the nonfamilial AF patients were deceased. At 10 years after the date of the AF diagnosis, 14.8% and 17.3% of the familial and nonfamilial AF patients, respectively, were deceased (Figure 2). In total, 1.6% of the patients with familial

Table 1. Baseline Demographics and Comorbidities by Family History of AF

	Familial AF (n=4329)	Nonfamilial AF (n=4329)	*P* Value
Demographics			
Female, n (%)	927 (21.4)	927 (21.4)	1.000
Median age (IQR)	50 (43–54)	50 (43–54)	1.000
Comorbidities, n (%)			
Alcohol abuse	84 (1.9)	116 (2.7)	0.026
Congenital anomaly of the heart	131 (3.0)	147 (3.4)	0.361
COPD	170 (3.9)	189 (4.4)	0.332
Diabetes mellitus	164 (3.8)	218 (5.0)	0.006
Heart failure	691 (16.0)	692 (16.0)	1.000
Heart valve disease	25 (0.6)	32 (0.7)	0.426
Hypertension	1174 (27.1)	1129 (26.1)	0.285
Ischemic heart disease	689 (15.9)	761 (17.6)	0.041
Nonischemic dilated cardiomyopathy	307 (7.1)	272 (6.3)	0.144
Peptic ulcer	243 (5.6)	296 (6.8)	0.021
Peripheral vascular disease	265 (6.1)	335 (7.7)	0.004
Prior shock or sepsis	187 (4.3)	272 (6.3)	<0.001
Renal disease	153 (3.5)	180 (4.2)	0.146
Stroke, TIA, or systemic thromboembolism	256 (5.9)	278 (6.4)	0.326
Thyroid disease	197 (4.6)	206 (4.8)	0.683
CHA_2DS_2-VASc*, n (%)			
0	2599 (60.0)	2532 (58.5)	0.155
1	750 (17.3)	766 (17.7)	
2	632 (14.6)	666 (15.4)	
≥3	348 (8.0)	365 (8.4)	
Median CHA_2DS_2-VASc* (IQR)	0 (0–1)	0 (0–1)	
Mean CHA_2DS_2-VASc* (SD)	0.74 (1.09)	0.77 (1.11)	

AF indicates atrial fibrillation; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; TIA, transient ischemic attack.
*Risk stratification scheme to assess stroke risk. CHA_2DS_2-VASc indicates congestive heart failure or left ventricular dysfunction; hypertension; age ≥75 years; diabetes mellitus; stroke, TIA, or systemic embolism; vascular disease; age 65–74 years; and sex category (female).

Table 2. Use of Pharmacotherapy at Baseline, Including All Dispensed Prescriptions From 3 Months Before the AF Diagnosis Until 7 Days After Discharge

Medications, n (%)	Familial AF (n=4329)	Nonfamilial AF (n=4329)	*P* Value
Adrenergic blockers	19 (0.4)	23 (0.5)	0.643
Antiplatelets*	616 (14.2)	700 (16.2)	0.013
Beta blockers	1654 (38.2)	1707 (39.4)	0.252
Calcium channel blockers	372 (8.6)	403 (9.3)	0.259
Class IC antiarrhythmic agents†	99 (2.3)	82 (1.9)	0.229
Class III antiarrhythmic agents‡	273 (6.3)	284 (6.6)	0.661
Digoxin	462 (10.7)	432 (10.0)	0.306
Diuretics	455 (10.5)	483 (11.2)	0.351
NOACs	125 (2.9)	120 (2.8)	0.796
NSAIDs	352 (8.1)	397 (9.2)	0.093
RAS inhibitors	764 (17.7)	785 (18.1)	0.575
Statins	405 (9.4)	505 (11.7)	<0.001
Thyroid medication	100 (2.3)	105 (2.4)	0.778
Vasodilators	42 (1.0)	36 (0.8)	0.570
Verapamil	157 (3.6)	120 (2.8)	0.028
Vitamin K antagonists	1027 (23.7)	904 (20.9)	0.002

NOACs indicates non–vitamin K antagonist oral anticoagulation; NSAID, nonsteroidal anti-inflammatory drugs; RAS, renin–angiotensin system.
*Includes adenosine diphosphate receptor antagonists and aspirin.
†Includes flecainide and propafenone.
‡Includes amiodarone, dronedarone, and sotalol.

AF and 1.7% of the nonfamilial AF patients had a thromboembolic event during the first year after the AF diagnosis. After 10 years of follow-up, 6.2% of the familial AF patients and 5.8% of the nonfamilial AF patients had a thromboembolic event. The median age at death was 53 years (IQR 47–57 years) for the familial AF group and 53 years (IQR 48–57 years) for the nonfamilial AF group. The analysis yielded a higher survival probability in familial AF patients compared with nonfamilial AF patients during follow-up (log-rank *P*=0.01). Figure 3 illustrates the cumulative incidence of thromboembolic events in patients with familial versus nonfamilial AF. No differences were seen between the 2 groups (*P*=0.51). Figure 4 shows the incidence rates and adjusted hazard ratios (HRs) of death and thromboembolism among patients with family history of AF compared with those without family history of AF. The crude HRs for death were significantly lower in familial AF patients compared with nonfamilial AF patients (HR 0.85, 95% CI 0.74–0.97), but after adjustment for covariates, no differences were seen between the familial and nonfamilial AF patients in terms of death (HR 0.91, 95% CI 0.79–1.04) and thromboembolism (HR 0.90, 95% CI 0.71–1.14). No interactions with ischemic heart disease, vascular disease, and diabetes mellitus were found for the main outcomes.

Premature Familial AF

Restricting the familial AF patient group to AF patients with a first-degree family member diagnosed with AF before age

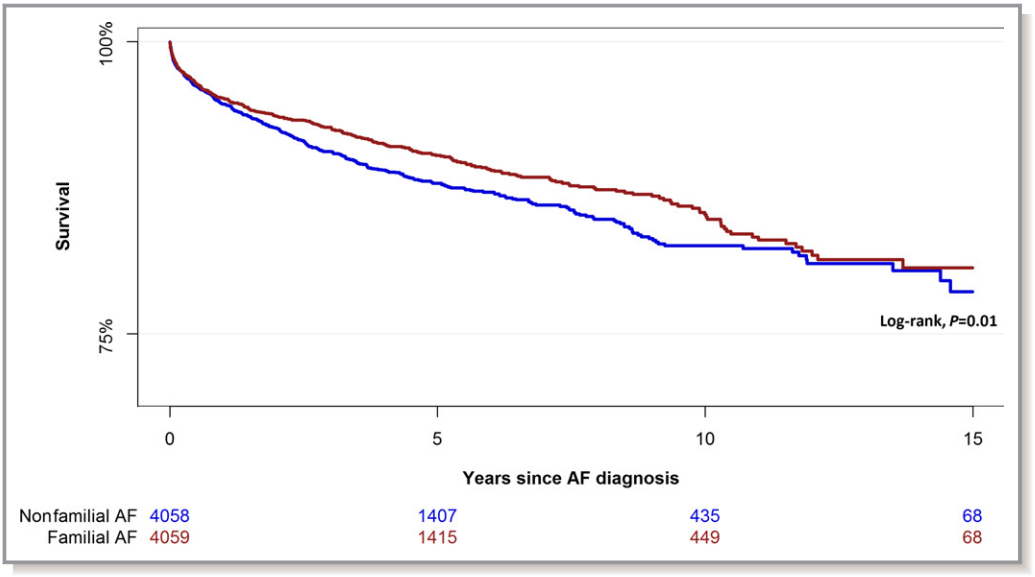

Figure 2. Kaplan–Meier curve for death by family history of atrial fibrillation (AF).

70 years resulted in a group of 2896 familial AF patients matched with the same number of nonfamilial AF patients. Figure 5 illustrates the incidence rates and crude and adjusted HRs of death and thromboembolic events by family history of AF. No differences were found between familial and nonfamilial AF patients regarding risk of thromboembolic events. Regarding all-cause mortality, the familial AF patients had a significantly lower risk of death compared with the nonfamilial AF patients (HR 0.83, 95% CI 0.69–0.99).

Discussion

This study examined a total of 8658 familial and nonfamilial AF patients who were matched into 4329 clinically similar pairs (same age at diagnosis, year of diagnosis, and sex). Our study yielded 4 main findings. First, familial AF was diagnosed at a young age. Second, ≈80% of patients with familial AF were men. Third, patients with familial AF had less comorbid illness than patients with nonfamilial AF. Fourth, after adjustments for comorbidities and concomitant pharmacotherapy, long-term clinical outcomes were similar for familial and nonfamilial AF patients.

Several studies have found the increased risk of AF in those with a family member diagnosed with AF to be dependent on the age of the family member at AF diagnosis; low age at AF diagnosis increases the risk of family members developing AF.[10–12,16] In previous work from the Outcomes Registry of Better Informed Treatment of Atrial Fibrillation

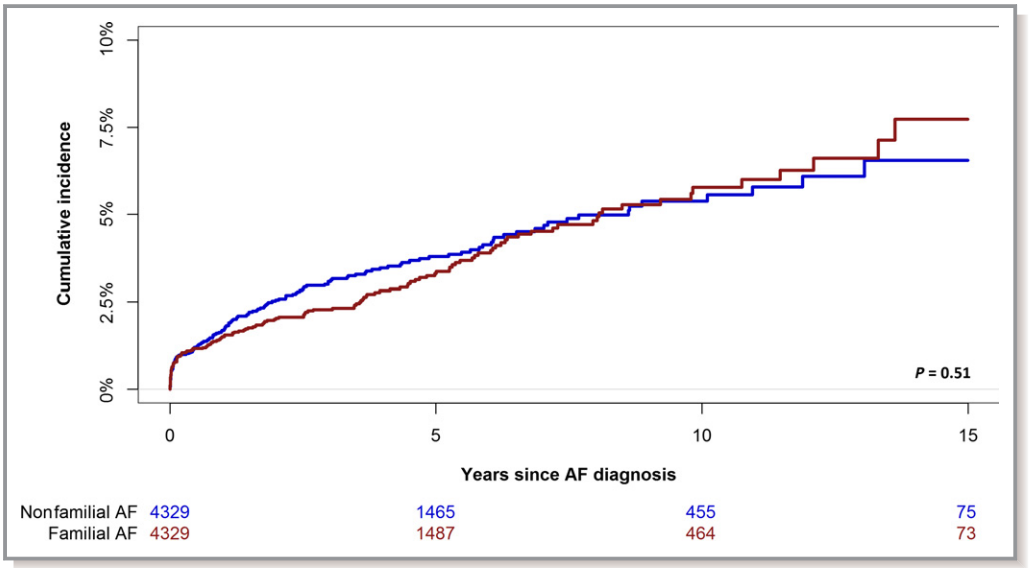

Figure 3. Cumulative incidence of thromboembolic events by family history of atrial fibrillation (AF).

Figure 4. Incidence rates and adjusted hazard ratios (HRs) of long-term outcomes (death and thromboembolic complications) according to family history of atrial fibrillation (AF). Covariates in the adjusted model: age at AF diagnosis, year of AF diagnosis, sex, comorbidities (including dementia; AIDS; stroke, transient ischemic attack, or systemic embolism; diabetes mellitus; heart valve disease; vascular disease; liver disease; thyroid disease; ischemic heart disease; renal disease; hemi- or paraplegia; peptic ulcer; congenital anomalies of the heart; chronic obstructive lung disease; rheumatic disease; cancer; prior shock or sepsis; arrhythmia; heart failure; alcohol abuse; and hypertension), and concomitant pharmacotherapy including nonsteroidal anti-inflammatory drugs, digoxin, corticosteroids, thyroid medication, statins, vitamin K antagonists, antithrombotic medication, non–vitamin K antagonists, class IC antiarrhythmic drugs, class III antiarrhythmic drugs, and verapamil. *Per 1000 person-years.

(ORBIT-AF), we compared familial and nonfamilial AF patients and found familial AF patients to be significantly younger at AF diagnosis than nonfamilial AF patients (median age 65 years [IQR 63–79 years] versus 70 years [IQR 61–77 years]).[17] In this study, the age difference was even more evident, with a median age at AF diagnosis for the familial AF patients of 50 years (IQR 43–54 years) compared with the nonfamilial AF patients, who had a median age at AF diagnosis of 77 years (IQR 67–84 years). This finding supports the hypothesis of a genetic predisposition to AF.

A study reporting the worldwide epidemiology of AF found a higher proportion of men diagnosed with AF compared with

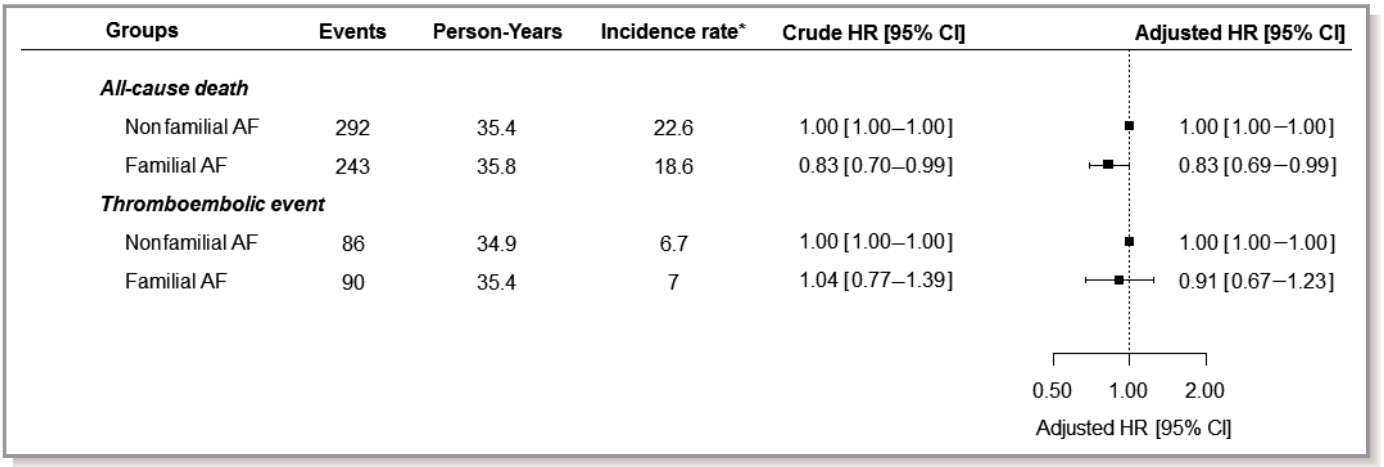

Figure 5. For premature familial atrial fibrillation (AF), incidence rates and adjusted hazard ratios (HRs) of long-term outcomes (death and thromboembolic complications) according to family history of atrial AF. Familial AF patients were defined as AF patients with a first-degree family member diagnosed with AF before age 70 years. Covariates in the adjusted model: age at AF diagnosis, year of AF diagnosis, sex, comorbidities (including dementia; aids; stroke, transient ischemic attack, or systemic embolism; diabetes mellitus; heart valve disease; vascular disease; liver disease; thyroid disease; ischemic heart disease; renal disease; hemi- or paraplegia; peptic ulcer; congenital anomalies of the heart; chronic obstructive lung disease; rheumatic disease; cancer; prior shock or sepsis; arrhythmia; heart failure; alcohol abuse; and hypertension), and concomitant pharmacotherapy including nonsteroidal anti-inflammatory drugs, digoxin, corticosteroids, thyroid medication, statins, vitamin K antagonists, antithrombotic medication, non–vitamin K antagonists, class IC antiarrhythmic drugs, class III antiarrhythmic drugs, and verapamil. *Per 1000 person-years.

women,[25] and the Framingham Heart Study found male sex to be an independent risk factor for developing AF.[26] In this study, only 21.4% of the patients were women, and in a study by Øyen et al including all lone AF patients in Denmark aged <60 years, 29.5% were women.[12] In contrast, almost half of the entire AF population in Denmark is composed of women (47%). The increasing population of especially elderly women may explain this sex difference across ages.

In the study from ORBIT-AF, we found familial AF patients to have less comorbid illness than nonfamilial AF patients, including chronic obstructive pulmonary disease and coronary artery disease. Despite this, no differences existed in median CHA_2DS_2-VASc scores between the 2 patient groups.[17] This finding is partly in accordance with our results in this report, in which we found lower prevalence of ischemic heart disease and several other comorbidities in patients with familial AF, whereas the 2 patient groups were comparable in terms of CHA_2DS_2-VASc score. In the ORBIT-AF study, the familial AF patients had less comorbidity but more symptoms than nonfamilial AF patients, and this result was independent of age. In this current study, it was not possible to compare symptom burden in the 2 patient groups.

We followed familial and nonfamilial AF patients for long-term follow-up and found that patients with familial AF had significantly lower crude risk of all-cause mortality compared with nonfamilial AF patients. The 2 patient groups were comparable regarding crude long-term risk of thromboembolic events. The crude increased risk of death for nonfamilial AF patients was expected because of the increased comorbidity in nonfamilial AF patients, and after multivariable risk adjustment, the difference was not statistically significant. The differences in risk of thromboembolic events in familial and nonfamilial patients remained insignificant after multivariable adjustment. Despite statistical nonsignificance, we cannot fully exclude the possibility of a difference in thromboembolic risk between familial and nonfamilial AF patients. In a selected sensitivity analysis, we restricted the group of familial AF patients to those with a first-degree family member diagnosed with AF before age 70 years. This did not change the results remarkably, but the risk of death became significantly lower among familial AF patients compared with nonfamilial AF patients, even in the adjusted analysis.

The recent acknowledgement of a familial form of AF should lead to considerations about the clinical course of familial AF and whether familial AF patients would benefit from another treatment strategy than the general AF population. We previously found that familial AF patients had more symptoms than nonfamilial AF patients.[17] In this study, the focus was on death and thromboembolic complications. We found no differences in the long-term risk of thromboembolic complications between familial and nonfamilial AF patients, but a trend was noted toward lower risk of death for familial AF patients compared with nonfamilial AF patients. Consequently, our results do not suggest different antithrombotic treatment approaches for familial AF patients and the general AF population.

In 2013, Christophersen et al reported a higher rate of death among AF patients with a twin diagnosed with AF compared with AF patients with a twin without AF.[27] In our previous work from ORBIT-AF, we found no differences in risk of death and thromboembolic complications in patients with and without familial AF. The present study is, to our knowledge, the first to examine the risk of death and thromboembolic complications during long-term follow up, and more studies are needed to further confirm these results. In addition, this study did not focus on specific genetic mutations associated with AF, and studies of genetic subgroups of familial AF and their long-term risk of complications are warranted.

This study has several limitations. First, we did not have relevant demographic variables such as blood pressure, body mass index, and race. In addition, no data about specific families, lifestyle factors, and familial hypertension were available. We also were not able to differentiate between paroxysmal, persistent, and permanent AF. The study was a retrospective registry study that did not allow for any causation to be drawn but rather only associations. In contrast, the Danish registries include complete and nationwide data and hold a unique and unselected sample of persons with complete information and many years of follow-up. Second, the registries included complete family information only from 1942 onward. This may have resulted in underestimation of patients with familial AF. Third, we ended up excluding the majority of the control group by excluding those without complete information about both parents. This was done to ensure that the controls did not have an unknown parent diagnosed with AF. Because the familial AF population was very young and because the complete registration of both parents improved over time, the remaining controls were young, and thus it was possible to do an almost complete 1:1 match of cases and controls without compromising the matching criteria. Fourth, the Danish National Patient Registry included only data from hospital contacts, and it is possible that some patients were diagnosed and treated by general practitioners. This may have caused some degree of selection bias, albeit minimal.

In conclusion, in a nationwide cohort, we found that familial AF was diagnosed at a younger age and more often in men compared with nonfamilial AF patients. Patients with familial AF had less comorbid illness than nonfamilial AF patients matched for age, year of diagnosis, and sex but did not differ significantly in their long-term adjusted risks of all-cause mortality and thromboembolic complications.

Disclosures

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SUPPLEMENTAL MATERIAL

Table S1. Specification of comorbidities by International Classification of Diseases (ICD), ICD-8 and ICD-10 codes

Comorbidity	ICD-8 and ICD-10 codes
Aids	ICD-8: 042-044 ICD-10: DB20-DB24
Alcohol abuse	ICD-8: 291, 303, 5710 ICD-10: DG312, DG621, DG721, DE24.4, DE52, DF10, DI426, DK292, DK70, DK860, DL278A, DO354, DZ714, DZ721
Arrhythmia	ICD-8: 4273-4275, 4276, 4279 ICD-10: DI46-DI49
Dementia	ICD-8: 290 ICD-10: DG30, DG311, DG312
Cancer	ICD-8: 140-195, 196-199, 200-209 ICD-10: DC00-DC97
Congenital anomaly of the heart	ICD-8: 74600-74799, 75900, 75901, 75909 ICD-10: DQ200-DQ289
Chronic Obstructive Pulmonary Disease	ICD-8: 490-492 ICD-10: DJ42, DJ44
Diabetes	ATC: A10 (3 months before to 7 days after the AF diagnosis)
Heart failure	ICD-8: 425, 4270, 4271 ICD-10: DI110, DI42, DI50, DJ819

Heart valve disease	ICD-8: 39500-39502, 39508, 39509, 39600-39604, 39608, 39609 ICD-10: DI05, DI06, DZ952, DZ954, DI080A, DI081A, DI082A, DI083A, KFKD, KFKH, KFMD, KFMH, KFGE, KFJF
Hemi- or paraplegia	ICD-8: 342, 344 ICD-10: DG041, DG81, DG82, DT144
Ischemic heart disease	ICD-8: 410-414 ICD-10: DI20-DI25
Liver disease	ICD-8: 456, 571, 572 ICD-10: DB150, DB160, DB190, DK70-DK77
Peptic ulcer	ICD-8: 531-534 ICD-10: DK221, DK25-27, K29
Renal disease	ICD-8: 582-586, 588 ICD-10: DI12, DI13, DN03, DN04, DN17-DN19, DR34, DT858, DT859, DZ992
Rheumatic disease	ICD-8: 7100, 7101, 7104, 7140-7142, 7148, 725 ICD-10: DM05, DM06, DM32-DM34, DM353
Shock or sepsis	ICD-8: 038, 7829 ICD-10: DA41, DR57
Stroke/TIA/systemic embolism	ICD-8: 433-435, 43601, 43690, 444

	ICD-10: DG458, DG459, DI63, DI64, DI74
Thyroid disease	ICD-8: 240-246 ICD-10: DE07
Vascular disease	ICD-8: 410, 440 ICD-10: DI21, DI70

Table S2. Specification of concomitant pharmacotherapy by Anatomical Therapeutic Chemical Classification (ATC)-codes (3 month before to 7 days after the AF diagnosis)

Pharmacotherapy	**ACT-codes**
Adrenergic blockers	C02A, C02B, C02C
Anti-thrombotic medication	B01AC04, B01AC06, B01AC22, B01AC22, B01AC24, N02BA01,
Beta blockers	C07A, C07B, C07C, C07D, C07F
Calcium channel blockers	C08, C07F, C09BB, C09DB
Class IC antiarrhythmic agents*	C01BC
Class III antiarrhythmic agents†	C01BD, C07AA
Corticosteroids	H02AB
Digoxin	C01A
Diuretics	C02DA, C02L, C03A, C03B, C03D, C03E, C03X, C07C, C07D, C08G, C09BA, C09DA, C09XA52
NOACs‡	B01AF01, B01AF02, B01AE07
NSAID§	M01A
RAS-inhibitors‖	C09AA, C09BA, C09BB, C09CA, C09DA, C09DB, C09XA02, C09XA52
Statins	C10AA
Thyroid medication	H03
Vasodilators	C02DB, C02DD, C02DG, C04, C05

Verapamil	C08DA
Vitamin K antagonists	B01AA03, B01AA04

[*]Includes flecainide and propafenone

[†]Includes amiodarone, dronedarone, and sotalol

[‡]Non-vitamin K antagonist oral anticoagulants

[§]Nonsteoridal anti-inflammatory drugs

[|]Includes angiotensin-2-inhibitors and ACE-inhibitors

Outcomes Associated With Familial Versus Nonfamilial Atrial Fibrillation: A Matched Nationwide Cohort Study

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