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Published in:
International journal of cardiology. Heart & vasculature

DOI:
10.1016/j.ijcha.2019.100429

Publication date:
2019

IJC Heart & Vasculature 25 (2019) 100429

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: www.journals.elsevier.com/ijc-heart-and-vasculature

Young-onset atrial fibrillation: Sex differences in clinical profile, progression rate and cardiovascular outcome ☆

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ARTICLE INFO

Article history:
Received 20 July 2019
Received in revised form 22 September 2019
Accepted 24 September 2019
Available online 7 November 2019

Keywords:
Atrial fibrillation
Young-onset
Sex
Cardiovascular outcome

ABSTRACT

Background: Women are underrepresented in major atrial fibrillation (AF) trials. In addition, data regarding clinical profile and outcome in young AF patients is limited. Therefore we aimed to investigate the clinical profile, AF progression rate and cardiovascular outcome between sexes in patients with young-onset AF.

Methods: A total of 497 patients with AF-onset <60 years of age were included. Data on clinical profile and cardiovascular outcome were prospectively collected.

Results: Of 497 patients, 125 (25%) patients were women. Women had more often familial AF (34% versus 22%, $P = 0.012$) and obesity (26% versus 18%, $P = 0.03$). Men had more often coronary artery disease (11% versus 5%, $P = 0.04$), a longer PR interval [163 (148–180) versus 150 (138–167) ms, $P < 0.001$] and higher left ventricular mass index [82 (71–96) versus 72 (61–83) g/m^2, $P < 0.001$]. During a median follow-up of 7.0 (2.7–10.0) years AF progression rate was comparable (HR 2.03 for men versus women, 95%CI 0.92–4.48; $P = 0.08$), and no difference in cardiovascular events was observed between women and men (Log rank P-value = 0.07).

Conclusions: In young patients with AF, clinical patient profile is different between the sexes but did not result in differences in cardiovascular outcome.

1. Introduction

Atrial fibrillation (AF) is strongly associated with morbidity and mortality [1]. Most data on AF is obtained from clinical trials, yet women are often underrepresented [2–4]. Limited data suggest that women are generally older and have different comorbidities, i.e. more often hypertension and less often coronary artery disease [2–4]. Additionally, sex is an independent stroke risk modifier that increases the risk of AF associated stroke in women. On top of higher stroke risk, stroke in women with AF have worse long-term outcome [5–7].

Data regarding underlying diseases in young patients with AF is rare, and may be different compared to older patients [8]. One would ideally like to identify underlying comorbidities early on in order to potentially prevent disease progression [9]. It has been shown that familial history of AF is often present in young-onset AF [8]. Whether there are risk factors that specifically affect women or men in young-onset AF has not yet been reported. Therefore we aimed to investigate sex-differences in clinical profile, AF progression rate and cardiovascular outcome in young-onset AF patients.

2. Methods

2.1. Study population

The protocol of the Phenotyping Young-Onset Atrial Fibrillation Patients study (YOUNG-AF) has been published previously [10]. In brief, YOUNG-AF was a partly prospective, partly retrospective, observational study performed at the University Medical Center Groningen, The Netherlands. Between August 2012 and December 2013, 500 patients were included. The study was performed in compliance to the Declaration of Helsinki and the institutional review board approved the study protocol. All patients provided written informed consent. At the outpatient clinic patients with AF onset <60 years, ≥18 years at time of inclusion were asked to participate. Patients with an overt triggered AF were excluded

☆ The authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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https://doi.org/10.1016/j.ijcha.2019.100429
2352-9067/

(i.e. post-operative). A total of 120 patients had first-detected AF, the remaining 377 patients had recurrent AF. In those patients, data regarding clinical profile was collected closest to the moment of the diagnosis of AF (index-visit). Follow-up frequency after the index-visit was led to the discretion of the treating physician and all patients received treatment according to the guidelines [11]. Three patients were excluded because of violation of the inclusion and exclusion criteria.

2.2. Definitions

The majority of definitions have been previously published [10]. Familial history of AF, sudden cardiac death, coronary artery disease or heart failure was defined as ≥1 first-degree family member affected <60 years of age. Atrial fibrillation progression was defined as development of permanent AF (i.e. sinus rhythm that cannot be restored or is no longer pursued). The number of comorbidities was calculated by awarding a point for hypertension; heart failure; diabetes mellitus; coronary artery disease; body mass index >25 kg/m^2; kidney dysfunction (estimated glomerular filtration rate <60 ml/min/1.73 m^2); and moderate to severe mitral valve regurgitation.

2.3. Follow-up

Data from electronic medical records were used to obtain information on AF progression and cardiovascular events, including cardiovascular death, heart failure hospitalization, stroke, systemic embolism, major bleeding, syncope, life-threatening adverse effects of AF drugs, sustained ventricular tachycardia, cardiac arrest and implantation of a pacemaker or implantable cardiac defibrillator. All cardiovascular events were adjudicated by physicians. Follow-up started at index-visit and was continued until February 2016 with a maximum of 10 years, or until death. Follow-up data was available in 488 out of 497 patients (98%). Data on AF progression was available in 468 (94%) patients with paroxysmal or persistent AF at the index visit.

2.4. Statistical analysis

Descriptive statistics of the total population and between sexes were presented as mean and standard deviation or median (interquartile range) for continuous variables, depending on normality. Categorical variables are presented as numbers with percentages. AF progression rate differences between sexes were calculated using univariable Cox proportional hazards regression, indicated as hazard ratios (HR) with 95% confidence interval (CI). Yearly event rates were calculated by dividing the number of follow-up years by the number of events, with censoring post first event. Differences in event rates and 95% CI were calculated by the MedCalc incidence rate comparison tool. Differences in patient characteristics between sexes were evaluated using χ^2 for categorical data, and Student's *T*-test and Mann-Whitney-U for continuous data, depending on the normality. A *P*-value <0.05 was considered significant. Kaplan Meier analysis was performed to illustrate cardiovascular events during follow-up. Statistical analyses were performed using IBM SPSS Statistics version 23.0 (Armonk, NY, USA) unless otherwise mentioned.

3. Results

3.1. Clinical patient profile

Out of 497 patients, 125 (25%) were women. Most conventional risk factors, including age, hypertension, heart failure and diabetes mellitus, were not different between sexes (Table 1). Women had more often familial AF and obesity. Men had more often coronary artery disease, a longer PR interval and higher left ventricular mass index. As expected, men were taller and heavier. There were no sex differences in familial history of sudden cardiac death, early-onset coronary artery disease or heart failure. Thirty patients were diagnosed with a cardiomyopathy, which was not different between sexes [12 (2%) hypertrophic; 17 (3%) dilated; and 1 (<1%) arrhythmogenic].

3.2. AF progression

AF progression to permanent AF was assessed in 468 patients with paroxysmal or persistent AF at the index visit [114 (24%) women]. Fifty-six patients (12%) had AF progression. Without correcting for underlying diseases, there was a trend towards more AF progression in men compared to women (14% in men, 7% in women; HR 2.02, 95%CI 0.92–4.48, *P* = 0.08). There were no differences in class I or III antiarrhythmic drug use during follow up between sexes [114 (31%) in men versus 42 (35%) in women, *P* = 0.500], nor in pulmonary vein isolations performed during follow-up [150 (41%) in men versus 51 (42%) in women, *P* = 0.832]. Corrected for antiarrhythmic drug use and pulmonary vein isolation performed during follow-up, progression rate remained similar between sexes (HR 1.93, 95% CI 0.88–4.28, *P* = 0.10).

3.3. Cardiovascular outcome

During follow-up of 7.0 [2.7–10.0; in men 7.6 (2.9–10.0) versus 6.4 (2.5–10.0) in women, *P* = 0.160] years, 66 cardiovascular events occurred (yearly event rate 2.24%, 95%CI 1.73–2.85%). No difference between sexes in the composite of cardiovascular events was observed [yearly event rate 2.76% (95%CI 1.71–4.22) in women; 2.01% (95%CI 1.46–2.70) in men, *P* = 0.07; Fig. 1]. Corrected for treatment during follow up, including the use of antiarrhythmic drugs and pulmonary vein isolation, the results remained (HR 1.91, 95% 0.86–4.24, *P* = 0.11). Occurrence of ventricular tachycardia was more frequent in women [yearly event rate 0.57% (95% CI 0.18–1.32%) versus 0.12% (95%CI 0.03–0.37%), *P* = 0.02]. Two out of 5 women used antiarrhythmic drugs at the time of VT. Also, a trend towards more pacemaker implantations in women was observed [1.34% (95%CI 0.67–2.39) versus 0.65% (95%CI 0.36–1.07); *P* = 0.06]. Sick sinus syndrome (50%), atrioventricular node conduction disorders (19%) and therapy resistant AF (31%) were causes for pacemaker implantation.

4. Discussion

We studied sex differences in clinical profile and cardiovascular outcome in young-onset AF patients. Women with young-onset AF had more often familial AF and obesity, whereas men had more coronary artery disease, a longer PR interval and higher left ventricular mass. We observed no difference in AF progression rate nor in cardiovascular outcome between sexes during 7-year follow-up.

In our prospective cohort, one out of four patients were women. AF is a rare disease in the young, and the probable misnomer 'lone AF' remains a diagnosis of exclusion [8–10]. Careful evaluation for cardiovascular risk factors should therefore be performed. Women had more often a family history of AF. Familial AF has been reported in 5–30% of patients [8]. Besides the genetic risk of AF itself, genetic susceptibility to other cardiovascular diseases may also play a role in the high rate of familial AF in young-onset AF [12]. Yet, many risk factors may remain subclinical and therefore

Table 1
Patient characteristics at index-visit of total population, and per sex category.

	All patients (n = 497)	Women (n = 125)	Men (n = 372)	*P*-value
Age at index-visit (years)	49 ± 9	51 ± 8	49 ± 9	0.057
Age at AF-onset (years)	46 ± 9	47 ± 9	46 ± 10	0.128
Type of AF				0.249
Paroxysmal	337 (68%)	89 (71%)	248 (67%)	
Persistent	140 (28%)	29 (23%)	111 (30%)	
Permanent	20 (4%)	7 (6%)	13 (4%)	
Heart failure	53 (11%)	10 (8%)	43 (12%)	0.317
Cardiomyopathy	30 (6%)	5 (4%)	25 (7%)	0.269
Hypertension	218 (44%)	52 (42%)	166 (45%)	0.603
Diabetes mellitus	25 (5%)	7 (6%)	18 (5%)	0.813
Coronary artery disease	47 (10%)	6 (5%)	41 (11%)	0.040
Peripheral artery disease	9 (2%)	2 (2%)	7 (2%)	0.838
Stroke or transient ischemic attack	30 (6%)	8 (6%)	22 (6%)	0.844
COPD	19 (4%)	7 (6%)	12 (3%)	0.279
Family history				
Familial AF	124 (25%)	42 (34%)	82 (22%)	0.012
Familial sudden cardiac death	48 (10%)	14 (11%)	34 (9%)	0.520
Familial coronary artery disease	109 (22%)	31 (25%)	78 (21%)	0.369
Familial heart failure	25 (5%)	7 (5%)	18 (5%)	1.000
CHA_2DS_2VASc score	1 (0–2)	2 (1–2)	1 (0–1)	<0.001
Number of comorbidities	1.3 ± 1.1	1.3 ± 1.1	1.4 ± 1.1	0.328
EHRA symptom class (n = 460)				0.508
I	46 (10%)	12 (10%)	34 (10%)	
II	337 (73%)	82 (69%)	255 (75%)	
III	73 (16%)	22 (18%)	51 (15%)	
IV	4 (<1%)	2 (2%)	2 (<1%)	
Height (cm)	182 ± 10	171 ± 7	185 ± 8	<0.001
Weight (kg)	92 ± 17	83 ± 20	94 ± 15	<0.001
BMI (kg/m^2)	27 (24–30)	28 (23–32)	27 (25–30)	0.446
Obesity (BMI > 30)	98 (20%)	33 (26%)	65 (18%)	0.030
PR interval (ms)	160 (144–176)	150 (138–167)	163 (148–180)	<0.001
Class I antiarrhytmic drug use	68 (14%)	22 (18%)	46 (13%)	0.131
Class III antiarrhytmic drug use	88 (18%)	20 (17%)	68 (18%)	0.684
Echocardiography				
Moderate or severe valve disease	39 (8%)	8 (6%)	31 (8%)	0.568
Left ventricular mass index (g/m^2)	80 (69–93)	72 (61–83)	82 (71–96)	<0.001
LA volume index (mL/m^2)	31 (25–31)	19 (23–32)	26 (21–32)	0.261
LVEF (%)	60 (55–60)	60 (55–60)	60 (55–60)	0.673

Data is expressed as mean and standard deviation, median (IQR) or numbers (%).
Abbreviations: AF = atrial fibrillation; BMI = body mass index; EHRA = European Heart Rhythm Association; LA = left atrial; LVEF = left ventricular ejection fraction. The number of comorbidities was calculated by awarding points for a history of hypertension, heart failure, diabetes, coronary artery disease, body mass index >25 kg/m^2, kidney dysfunction and moderate or severe mitral valve disease.

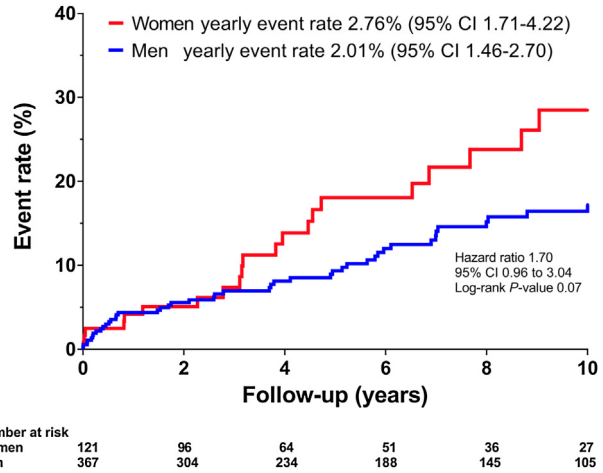

Fig. 1. Kaplan Meier curve illustrating the cumulative incidence of cardiovascular events during follow-up.

untreated for years. In fact, AF might be the first clinical presentation of an underlying cardiomyopathy. The number of cardiomyopathies was, however, still low in our population. Of interest is the relatively high number of reported familial sudden cardiac death, which may be due to underlying cardiomyopathies or other untreated cardiovascular (genetic) diseases.

Identification and treating risk factors and comorbidities is important in AF treatment, and preventing progression of atrial remodeling [9,13]. We observed no difference in AF progression rate between sexes. AF progression is a complex process mainly driven by comorbidity and ageing related atrial remodeling [14]. The equal number of comorbidities and similar age between men and women in our cohort may have contributed in finding similar progression rate.

Obesity, a modifiable risk factor for AF, was observed more often in women [15,16]. Obesity has been associated with a prothrombotic state [17,18]. On top of that, obesity-related cardiac remodeling, including epicardial adipose tissue infiltration, inflammation and fibrosis, enhances AF substrate formation, also causing AF to progress and sustain [18]. The higher incidence of coronary artery disease in men is well known. It should therefore always be considered causal factor associated with AF – especially in men. Even in patients diagnosed with idiopathic AF, half showed coronary artery disease as assessed by noninvasive imaging [19]. PR interval and left ventricular mass were both higher in men compared to women. Both have previously been associated with cardiovascular outcome in patients with AF [10].

Women with AF may have worse cardiovascular outcome, yet women tend to be older and have more comorbidities [3]. We found no sex difference in cardiovascular outcome in our young-onset AF cohort, which can be partially accounted to the relatively low number of events in general due to the young age. Yet, a trend was observed towards a higher event rate in women, especially after 3 years of follow-up, which could be related to differences in underlying disease in men and women.

5. Limitations

Strengths of present study include a well-characterized cohort and unique dataset of young-onset AF patients. Whether the associations that were found reflect cause-effect relationships cannot be concluded from our data, which may be considered a limitation, as well as the limited number of cardiovascular events. A time-to-event analysis was performed for AF progression to permanent AF without structured rhythm monitoring during follow-up, limiting its accuracy. Because of this, we were also unable to determine progression from paroxysmal to persistent AF. Furthermore we did not have follow-up data on blood pressure and weight, limiting our knowledge on risk factor management in our population.

6. Conclusion

The clinical profile between men and women with young-onset AF is different. We observed no differences in AF progression rate between men and women, nor differences in cardiovascular outcome.

Funding

We acknowledge the support from the Netherlands Cardiovascular Research Initiative: an initiative with support of the Dutch Heart Foundation, CVON 2014-9: Reappraisal of Atrial Fibrillation: interaction between hyperCoagulability, Electrical remodeling, and Vascular destabilisation in the progression of AF (RACE V). Grant support to the institution from Medtronic outside submitted work. The authors report no conflicts of interest.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2019.100429.

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