Family history of atrial fibrillation and risk of cardiovascular events.

A multicenter prospective cohort study.

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Abstract

OBJECTIVE. To investigate the association between family history of atrial fibrillation (AF) with cardiovascular events (CVEs), major adverse cardiac events (MACE) and cardiovascular mortality.

PATIENT AND METHODS. Multicenter prospective observational cohort study including 1,722 non-valvular AF patients from February 2008 to August 2019 in Italy. Family history of AF was defined as the presence of AF in a first-degree relative: mother, father, sibling, or children. Primary outcome was a composite of CVEs including fatal/non-fatal ischemic stroke and myocardial infarction, and cardiovascular death. Second, we analyzed the association with MACE.

RESULTS. Mean age was 74.6±9.4 years; 44% of women. Family history of AF was detected in 368 (21.4%) patients, and 3.5% had ≥2 relatives affected by AF. Age of onset of AF progressively decreased from patients without family history AF, compared to those with single and multiple first-degree affected relatives ($p<0.001$). During a mean follow-up of 23.7 months (4,606 patients/years) 145 CVEs (3.15%/year), 98 MACE (2.13%/year) and 57 cardiovascular deaths (0.97%/year) occurred. After adjustment for cardiovascular risk factors, family history of AF was associated with a higher risk of CVEs (hazard ratio [HR] 1.524, 95% confidence interval [CI] 1.021-2.274, p=0.039) MACE (HR 1.917, 95%CI 1.207-3.045, p=0.006) and cardiovascular mortality (HR 2.008, 95%CI 1.047-3.851, p=0.036). Subgroup analysis showed that this association was modified by age, sex and prior ischemic heart disease.

CONCLUSION. In a cohort of elderly patients with a high atherosclerotic burden, family history of AF is evident in >20% of patients and was associated with an increased risk for CVEs and mortality.

Keywords: Atrial fibrillation, family history of AF, Cardiovascular events, Mortality, New onset atrial fibrillation, MACE

Introduction

Patients with atrial fibrillation (AF) are at increased risk of cardiovascular and cerebrovascular ischemic complications [1-3] and mortality[4]. Several risk factors may predispose to new-onset AF[5, 6]. Data from the Atherosclerosis Risk in Communities (ARIC) study showed that 56.5% of new-onset AF may be attributed to coexistent risk factors[7, 8]. They include modifiable risk factors, such as uncontrolled arterial hypertension, thyroid dysfunction, obesity, excessive alcohol consumption, sleep apnea syndrome and anticoagulation treatment[9], and non-modifiable risk factors including increasing age, congenital heart disease, severe valvulopathy, cardiac surgery and genetic predisposition[7, 8]. Concerning the latter aspect, genome wide association studies have identified several genetic susceptibility loci associated with AF[10], including mutations in ion channels expressed in atria or ventricles possessing electrophysiological properties. Nevertheless, the translational value of these findings remains unclear, and genetic screening is not performed for all patients in everyday clinical practice[11].

Beyond complex genetic studies, family history of AF, as defined by the presence of AF in a first-degree relative, has been shown to confer an increased risk of early onset AF[12-16]. In a Danish population study, for example, the adjusted relative risk for incident AF was 3.37 [95% confidence interval (CI) 3.21–3.53] for the offspring from maternal probands, and 2.81 (95% CI 2.69–2.93) for offspring from paternal probands[17]. Furthermore, patients with persistent AF and a family history of AF had a higher recurrence after catheter ablation[18]. However, the association between family history of AF and clinical outcomes is more controversial, with studies reporting negative[15, 19] or positive[20] associations.

In this multicenter prospective observational cohort study, our aim was to investigate the prevalence of family history of AF, and second, to compare the incidence rate of cardiovascular events (CVEs), major adverse cardiac events (MACE) and cardiovascular mortality according to the presence of family history of AF.

Materials and methods

Data and methods used in the analysis will be available for researchers upon reasonable request.

We established a multicentre, prospective, observational cohort study, which included 1,722 AF Caucasian outpatients from the ATHERO-AF cohort at "Sapienza" University of Rome and from "Magna Graecia" University of Catanzaro. The ATHERO-AF study started in February 2008 and is still ongoing (clinicaltrials.gov NCT01882114); for this analysis, follow-up was stopped at August 2019.

The study included patients with both VKAs and NOACs. All patients were treated with oral anticoagulants, either VKAs (n=948) or non-VKA oral anticoagulants (NOACs, n=774). During the first clinical examination a completed personal medical history was collected, including drug therapy and comorbidities. The presence of AF was defined by resting 12-lead electrocardiogram; for patients with paroxysmal AF in sinus rhythm, a clinical documentation showing the presence of AF was collected. Patients were also asked about the age when AF was first diagnosed.

Exclusion criteria were prosthetic heart valves, or the presence of any severe valvulopathies, severe cognitive impairment, chronic infections (Human Immunodeficiency Virus infection, Hepatitis C virus, Hepatitis B virus) or systemic autoimmune diseases. Subjects were also excluded from the study if they had active cancer or liver insufficiency (eg, cirrhosis).

Definition of cardiovascular comorbidities

Definitions of cardiovascular risk factors have been previously reported[21]: Arterial hypertension: repeatedly elevated blood pressure (≥140/≥90 mmHg) or taking antihypertensive-drugs[22]. Diabetes: a casual plasma glucose ≥200 mg/dl (11.1 mmol/l), or fasting plasma glucose ≥126 mg/dl (7.0 mmol/l), or 2-h plasma glucose ≥200 mg/dl (11.1 mmol/l) during an oral glucose tolerance test or taking anti-diabetic drugs[23]. Heart failure: presence of signs and symptoms typical of heart failure or reduced ejection fraction (≤40%)[24].

All patients signed an informed written consent at study entry. The study was approved by the local ethic committee of "Sapienza" University and was conducted according to the declaration of Helsinki.

Follow-up and definition of primary outcome

Follow-up was performed by periodic clinical evaluations or by telephone if patients missed 1 or more visit. For patients on VKAs, follow-up visit was scheduled at the anticoagulation clinic

according their value of INR, and in any case, the longest period between two controls did not exceed 20 days. For patients on NOACs, patients after first prescription were visited at the outpatient clinic after 1, 3, 6 and 12 months according to ESC indications, and every 6-12 months afterwards.

Definition of clinical endpoints

Only the first event occurred during the follow-up was used for the analysis. Data of patients who were lost during follow-up were censored.

CVEs were defined as fatal/non-fatal ischemic stroke and MI, cardiac revascularization/coronary bypass surgery, cardiovascular death and transient ischemic attack (TIA). The diagnosis of MI was formulated according to the universal definition proposed by the Joint ESC/ACCF/AHA/WHF[25]. If a patient died within 4 weeks of a stroke or heart attack, this event was recorded as fatal. Death was classified as cardiovascular unless a non-cardiovascular cause of death was identified. Cardiovascular death included sudden death, progressive heart failure, death related to surgical or percutaneous revascularization procedures. The diagnosis of ischemic stroke was determined by clinical manifestations then confirmed by radiological findings. The TIA was defined according to the Classification of cerebrovascular disease III[26]. Only the first event was used for the analysis, and confirmation of the primary event was made by a blinded commission that did not participate in patient recruitment and was not aware of the characteristics of any of the enrolled patients. We also analyzed the occurrence of MACE, which consisted of fatal-nonfatal MI, cardiac revascularization and cardiovascular death (excluding fatal and non-fatal stroke and TIA).

Validation of endpoints

Data on CVEs, MACE and CV death were prospectively collected during follow-up. When an event occurred, a standardized form was filled in by the investigators. Details on each event were registered, as well as death certificates, hospital discharge letter or copy of the medical records of hospitalization, and other clinical documentation (i.e. radiology and laboratory data) were also obtained from patients, or in case of death, from relatives of patients or from general practitioner. Adjudication of cardiovascular events was performed by a committee composed by physicians who did not participate to the recruitment of patients and was unaware of the clinical and laboratory characteristics of any enrolled patient. Each member of the committee independently evaluated and adjudicated events in a blinded manner. In case of discordant evaluation or difficult adjudication of an event, the committee decided to award the event in a collegial way.

Definition of family history of AF

Family history of AF was defined as the presence of AF in at least one first-degree relative among mother, father, siblings or children. Multiple family history of AF was defined as the presence of AF in 2 or more relatives. These data were recorded during the first visit by a trained physician by direct face-to-face interview with patient and relatives when available. Patients were asked if they knew about cases of AF in the first-degree relatives, and relatives were also interviewed. In addition, as confirmation, they were also asked if someone of the relatives was taking anticoagulant drugs. Patients who were not sure about these questions were excluded. Relatives of patients have not been included in the study cohort.

Statistical analysis

Categorical variables were reported as a number or percentage and compared by the Pearson's χ^2 test. Continuous variables were expressed as mean ± standard deviation and Student t-test was used to compare means. We divided the cohort into 2 groups based on the presence/absence of family history of AF and we performed a descriptive analysis of groups characteristics. Annual incidence rates of each endpoint were calculated. Multivariable proportional hazard Cox regression analysis was used to estimate the relative hazard ratio (HR) with 95% confidence interval (95%CI) for each variable. The following variables were entered as covariates in the multivariable model: age >75 years, age of AF onset (years), persistent/permanent AF (vs. paroxysmal), women, arterial hypertension, diabetes mellitus, previous cerebrovascular events, heart failure, and previous ischaemic heart disease.

We built three separate survival models for: (i) CVEs; (ii) MACE (excluding thromboembolic events); and (iii) cardiovascular deaths. Adjusted survival curves were displayed according to the presence of family history of AF. Subgroup analysis by sex, age > 70 or ≤ 70 years, and prior cardiovascular disease was also performed.

Only p-values below 0.05 were considered statistically significant. All the tests used are two-sided and the analyses were performed using electronic software packages (SPSS-25.0, SPSS Inc., IBM Corp., Armonk, NY, USA; license provided by Sapienza University of Rome).

Results

Patient characteristics according to study groups are summarised in **Table 1.** We included 1,722 anticoagulated AF patients (mean age 74.6 ± 9.4 years; 44% female). In the cohort there was a high prevalence of atherosclerotic risk factors, with a high prevalence of arterial hypertension (87.2%), diabetes mellitus (21.7%), and previous cardiovascular and cerebrovascular ischemic events (17.3% and 14.5%) (**Table 1**).

A family history of AF was detected in 368 (21.4%) patients. Of these, 3.5% had more than one first-degree family member with AF **(Figure 1, Panel A)**. The relatives that were most frequently affected by AF were siblings (51.9%), followed by parents (32.3% and 21.2%, mother and father respectively) and children (6.8%), as shown in **Figure 1, Panel B**.

Patients with family history of AF were younger than those without but no other significant difference regarding cardiovascular risk factors was found (**Table 1**). Of note, the age of onset of AF progressively decreased from patients without familial history, to those with single and multiple first-degree relatives affected, as shown in **Figure 2** ($p<0.001$).

Survival analysis

Cardiovascular events.

During a mean follow-up of 23.7 months (yielding 4,606 patients/years) 145 CVEs occurred (3.15%/year) and 39 patients were lost and other 14 were censored because newly diagnosed with cancer. On multivariable Cox regression analysis (**Table 2**), family history of AF was an independent predictor for CVEs, after adjustment for traditional cardiovascular risk factors. Further independent risk factors for CVEs were age ≥75 years, heart failure, previous ischaemic heart disease, previous IS/TIA and age of AF onset (**Table 2)**. **Figure 3, Panel A** shows the adjusted survival probability free from CVEs of patients with and without family history of AF.

Major adverse cardiovascular events (MACE).

The MACE endpoint (excluding thromboembolic events) occurred in 98 patients (2.13%/year). On multivariable Cox proportional regression analysis, we found that the family history of AF was independently associated with MACE occurrence **(Table 3).** Other risk factors for MACE were the presence at baseline of heart failure, a history of ischemic heart disease and the age of onset of AF **(Table 3)**. **Figure 3, Panel B** shows the adjusted survival probability free from MACE of patients with and without family history of AF.

Cardiovascular death.

In our cohort, 57 cardiovascular deaths occurred (0.97%/year). On multivariable Cox survival analysis (**Table 2**) family history of AF was an independent predictive risk factor for cardiovascular death, together with age of onset of AF, heart failure and previous ischaemic heart disease. **Figure 3, Panel C** shows the adjusted survival probability free from cardiovascular death of patients with and without family history of AF.

Subgroup analysis

Similar results were obtained using age as continuous variable for all the three endpoints considered (Supplementary table 1).

A subgroup analysis according to age, showed that the association between family history of AF and risk of CVEs, MACE and CV death was evident in patients aged >70 years but not in those ≤70 years (**Table 3**). When we divided patients according to prevalent cardiovascular disease, we found that the association between family history of AF and risk of CVEs, MACE and CV death was evident only in patients with prior coronary artery disease. Finally, when analysis by sex, showed a significant association between family history of AF with MACE and CV death in men but not in women (**Table 3**).

Discussion

In this multicenter prospective observational cohort study, our principal finding was that more than 20% of patients with AF have a first-degree relative suffering from the same arrhythmia. Second, the presence of family history of AF was associated with an increased risk of CVEs, MACE and cardiovascular mortality.

The data from our work agree with the previous studies that also reported that the presence of family history of AF was a risk factor for early new-onset AF compared with patients without a family history of AF[12, 27, 28]. We also found that when ≥2 first-degree relatives had AF, the age of onset of AF was even lower than patients with only one affected family member (62 vs. 67 years, respectively).

In the present study, which included Caucasian elderly AF patients with multiple atherosclerotic risk factors, family history of AF was associated with an increased risk of ischemic complications, such as CVEs, MACE and cardiovascular mortality.

Our findings are partially in contrast with previous studies on this subject. For example, a Danish retrospective study showed no difference in mortality and thromboembolic risk in patients with and without family history of AF[19]. However, some important differences between our study and the Danish cohort may potentially account for this difference. For instance, the mean age of the Danish patients was 50 years, compared to 75 years in the present study; moreover, only 20% of that study were female, and there was a very low prevalence of cardiovascular risk factors compared to our cohort (eg. hypertension 27.1% vs 87.2% and diabetes 3.8% vs. 21.7%, respectively)[19]. A more recent large study from Taiwan included 244,067 patients with AF, and also showed no association between family history of AF and risk of MACE[15]. Even in this study, the majority of patients were relatively young (82.1% were aged <65 years), only 13.6% of female, and 34.5% were hypertensive[15].

What should also be taken into consideration is that all patients in our study were anticoagulated, whilst in both of the two studies mentioned above, there was a very low proportion of patients was on treatment with oral anticoagulants: for example, <30% in the Danish cohort[19] and <3% in the Taiwan study[15]. This may have affected the rate of cardiovascular events registered in the studies. Finally, one large Canadian study showed that the incidence rates for stroke/TIA were higher in offspring with a parental history of AF than those without (195.0 vs. 156.6 per 100 000 person-years)[20]. Also, parental AF was also associated with elevated risk in offspring of stroke/TIA (HR 1.11; 95% CI, 1.04–1.18) or AF (HR 1.75; 95% CI, 1.55–1.97)[20].

Our study has clinical implications. The significantly lower age of onset of AF in patients with single and multiple family history of AF implies that subjects with a first-degree suffering from AF should be advised to perform screening and clinical evaluation to detect new-onset AF. This may lead to a potential saving of health-related costs related to AF complications[29]. The age of onset of AF in our study, likely representing the length of the disease since AF was first diagnosed, was independently associated with the ischemic risk, again reinforcing the need for early screening of relatives of patients affected by AF.

Furthermore, the significant association between family history of AF and outcomes may represent a new risk factor which may easily be obtained by an accurate interview of the patient during the first visit. This information may turn particularly useful in some subgroups of patients, such as those in whom the choice whether to start or not an oral anticoagulation treatment is uncertain. Thus, the presence of a family history of AF, especially if multiple, may help physician in the decision-making process.

Subgroup analysis showed that the association between family history of AF and cardiovascular outcomes is strongly modified by sex, age and prevalent cardiovascular disease, underlying that there is complex interaction between polygenic factors, demographic characteristics and environmental variables. In particular, we did not find a significant difference in the proportion of women between the two groups of patients with and without family history of AF, which is in contrast with a previous study on 5,884 AF patients from the Health eHeart Study[30]. Female sex was not associated with cardiovascular outcomes in our study, differently from findings from the RACE II trial in which female sex was associated with the composite of CVEs but not with increased cardiovascular death[31]. Of interest, the association between family history and outcomes was stronger in women than men, suggesting a sex-based difference. Further study on the relationship between family history of AF and sex are needed.

The mechanisms underlying our results may be several. The similar baseline cardio-metabolic characteristics of patients with and without family history of AF suggest that other variables than the traditional cardiovascular risk factors may confer an increased risk of both early onset of AF and of cardiovascular events in these patients. These aspects may pertain structural and electrophysiology characteristics, as suggested by documented genetic-based alterations in some proteins like myosin[32] or ion channels[33]. It would be therefore interesting to study heart structure and function as well as electrical conduction in patients with family history of AF. Genome sequencing of patients with family history may also provide novel insights on this topic and may help to better characterize risk profile of these patients[34].

The burden of family history seems also to influence the risk of AF, as shown by individuals with ≥1 affected parent and ≥1 affected sibling in whom the odds ratio for having new AF was 5.56 (95% CI 4.99 to 6.20). This is in keeping with our study in which patients with multiple relatives affected by AF have a lower age of onset of AF compared to those with only 1 or none affected relative[35].

Limitations

Our study has limitations. First, this is an observational study, and it is not possible to establish a cause-effect relationship between the presence of family history of AF and the onset of ischemic complications. Second, the presence of family history of AF was recorded through a direct face-to-face interview with the patient and with relatives (when available), and although performed by dedicated staff, may still present inaccuracies in recording of familial disorders. However, when patients or relatives were not sure about the type of cardiac disorder, these were excluded. Furthermore, we cannot exclude that other factors/diseases may contribute to the onset of AF in relatives of patients. Third, our data comes from a cohort of all Caucasian elderly patients, thus the prevalence and impact on outcomes cannot be applied to populations of other ethnic groups. Fourth, the cohort was composed by patients enrolled in a hospital-based anticoagulation clinic. Finally, we did not investigate differences in the association between single or multiple family history of AF links and ischemic complications, due to the limited number of patients with multiple family history. Similarly, larger studies are needed to analyse the relationship between different type of family history of AF (i.e. mother or father) and CVEs.

Conclusion

In a cohort of elderly patients with a high atherosclerotic burden, family history of AF is evident in >20% of patients and was associated with an increased risk for CVEs and mortality. First-degree relatives of patients with AF should undergo screening and clinical evaluation to detect new-onset AF and appropriate cardiovascular prevention strategies.

Authors' contribution:

DP and PP contributed to the conception or design of the work.

DM, AS, PP contributed to the acquisition, and interpretation of data for the work.

DP contributed the analysis of data

DP, GYHL, FV, PP, AS and DM drafted the manuscript.

DP, FV, GYHL and PP critically revised the manuscript.

All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Figures legend

Figure 1. Panel A. Prevalence of single and multiple familiarity for atrial fibrillation (AF) in first degree relatives in the whole cohort. Panel B. Prevalence of different types of familiarity.

Figure 2. Age of onset of atrial fibrillation in patients without and in those with single and multiple family history of AF.

Figure 3. Adjusted Cox survival curves in patients with and without family history of AF for cardiovascular events (Panel A), major adverse cardiovascular events (MACE, Panel B) and cardiovascular death (Panel C).

Table 1. Characteristics of the study population according to the presence of familial atrial fibrillation.

	Total (n=1,722)	Patients without family history AF (n= 1,354)	Patients with family history AF (n= 368)	p-value*
Age (years)	74.6±9.4	75.2±9.22	72.3±9.73	<0.001#
Age >75 years (%)	52.2	54.2	44.8	0.001§
Age of AF onset (years)	69.9±11.6	70.8±11.6	66.3±10.88	<0.001#
Persistent/permanent AF (%)	56.4	57.3	53.4	0.192§
Women (%)	49.9	49.2	52.9	0.217§
NOAC (vs VKAs)	44.9	44.5	46.7	0.443§
Arterial hypertension (%)	87.2	87.4	86.6	0.724§
Diabetes mellitus (%)	21.7	22.1	19.9	0.391§
Previous cerebrovascular events (%)	14.5	14.8	13.4	0.558§
Heart failure (%)	16.3	16.8	14.4	0.297§
Previous ischaemic heart disease (%)	17.3	17.2	17.6	0.876§
CHA_2DS_2VASC score	3.5±1.5	3.54±1.48	3.35±1.54	0.026#

AF: atrial fibrillation, NOAC: non-vitamin K anticoagulants, VKA: vitamin K antagonist

***comparing familial vs. non-familial group; # student t test; § χ^2 test**

Table 2. Multiple Cox regression analysis of risk factors for cardiovascular events (Panel A), major adverse cardiovascular events (Panel B), and cardiovascular death (Panel C).

Panel A. CVEs	Hazard Ratio	95% Confidence Interval		p-value
		Lower	Upper	
Age ≥ 75 years	**1.60**	**1.02**	**2.50**	**0.042**
Persistent/permanent AF	0.88	0.62	1.23	0.442
Age of AF onset	**1.04**	**1.02**	**1.07**	**0.002**
Female	0.78	0.55	1.10	0.159
Arterial hypertension	1.12	0.58	2.15	0.733
Diabetes mellitus	1.24	0.85	1.79	0.265
Heart failure	**1.90**	**1.30**	**2.78**	**0.001**
Previous cerebrovascular events	**1.98**	**1.35**	**2.88**	**<0.001**
Previous ischaemic heart disease	**1.73**	**1.20**	**2.49**	**0.003**
Family history of AF	**1.52**	**1.02**	**2.27**	**0.039**
Panel B. MACE (excluding thromboembolism)	**Hazard Ratio**	**95% Confidence Interval**		**p-value**
		Lower	**Upper**	
Age ≥ 75 years	1.32	0.76	2.28	0.321
Persistent/permanent AF	1.00	0.66	1.52	0.996
Age of AF onset	**1.05**	**1.02**	**1.08**	**0.002**
Female	0.80	0.52	1.21	0.287
Arterial hypertension	1.30	0.57	3.00	0.535
Diabetes mellitus	1.16	0.74	1.83	0.521
Heart failure	**2.18**	**1.40**	**3.41**	**0.001**
Previous cerebrovascular events	1.47	0.90	2.40	0.126
Previous ischaemic heart disease	**1.98**	**1.28**	**3.06**	**0.002**
Family history of AF	**1.92**	**1.21**	**3.05**	**0.006**
Panel C. Cardiovascular death	**Hazard Ratio**	**95% Confidence Interval**		**p-value**
		Lower	**Upper**	
Age ≥ 75 years	1.65	0.73	3.72	0.227
Persistent/permanent AF	1.32	0.74	2.37	0.348
Age of AF onset	**1.10**	**1.05**	**1.15**	**<0.001**
Female	0.72	0.42	1.26	0.253
Arterial hypertension	4.21	0.58	30.58	0.155
Diabetes mellitus	1.39	0.77	2.50	0.275
Heart failure	**2.18**	**1.22**	**3.90**	**0.008**
Previous cerebrovascular events	1.65	0.90	3.04	0.106
Previous ischaemic heart disease	**1.81**	**1.02**	**3.21**	**0.044**
Family history of AF	**2.01**	**1.05**	**3.85**	**0.036**

AF: atrial fibrillation; CVEs: cardiovascular events; MACE: major adverse cardiac events

Table 3. Adjusted hazard ratio (95% confidence interval) for family history of AF according to specific subgroups of patients.

	CVEs	MACE	CV death
Age > 70 years	1.58 (1.00-2.50)	1.83 (1.07-3.14)	2.15 (1.06-4.37)
Age ≤ 70 years	1.24 (0.55-2.81)	2.20 (0.85-5.70)	1.16 (0.21-6.46)
Men	1.39 (0.80-2.41)	1.46 (0.80-2.80)	1.72 (0.71-4.18)
Women	1.74 (0.95-3.17)	3.04 (1.52-6.11)	2.69 (1.01-7.22)
Prior cardiovascular disease	2.11 (1.15-3.88)	2.85 (1.44-5.65)	3.06 (1.21-7.77)
No prior cardiovascular disease	1.22 (0.70-2.10)	1.36 (0.70-2.62)	1.26 (0.47-3.37)

CV: cardiovascular, CVEs: cardiovascular events, MACE: major adverse cardiac events

Covariates were the same used in table 2 (excluding the variable used to categorize results).

Figure 1.

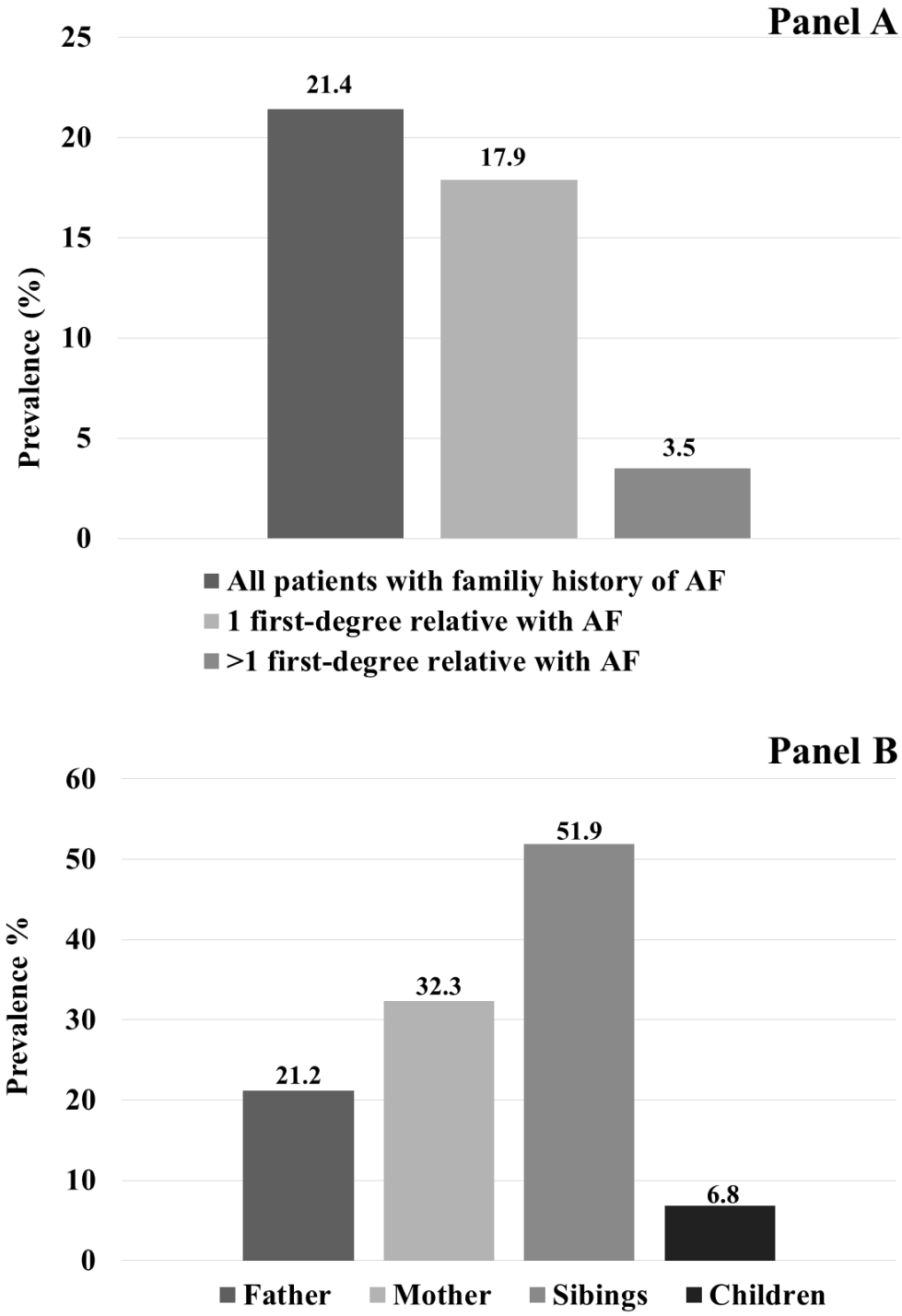

Panel A
25
20
15
10
5
0
Prevalence (%)
21.4
17.9
3.5
All patients with familiy history of AF
1 first-degree relative with AF
>1 first-degree relative with AF
Panel B
60
50
40
30
20
10
0
Prevalence %
21.2
32.3
51.9
6.8
Father
Mother
Sibings
Children

Figure 2.

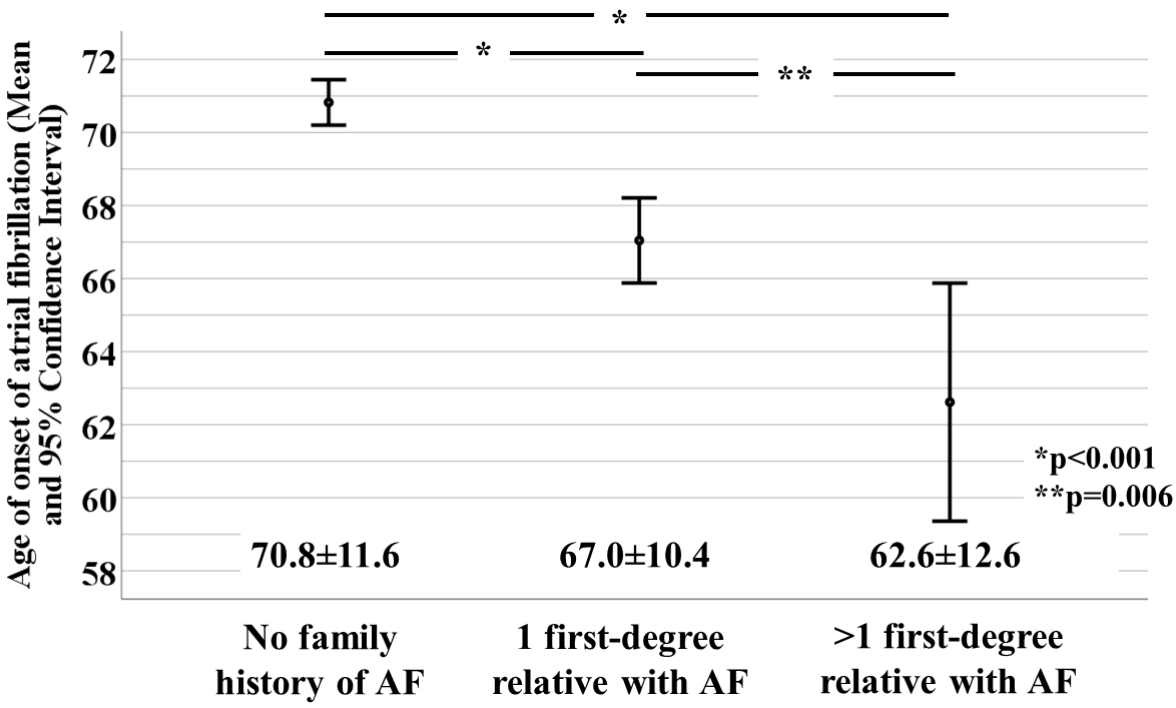
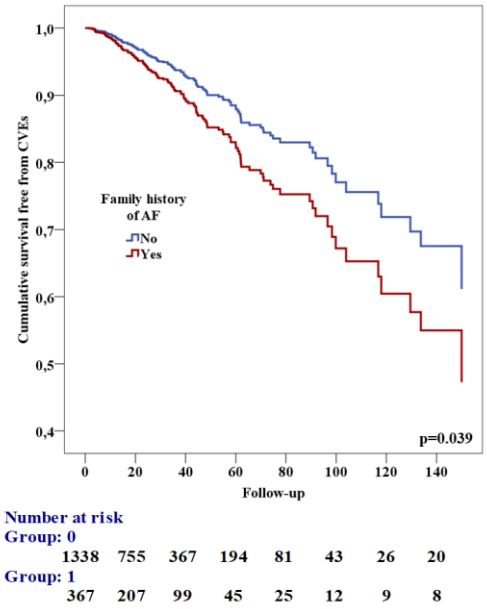

Age of onset of atrial fibrillation (Mean and 95% Confidence Interval)
72
70
68
66
64
62
60
58
*
*
**
*p<0.001
**p=0.006
70.8±11.6
67.0±10.4
62.6±12.6
No family history of AF
1 first-degree relative with AF
>1 first-degree relative with AF

Figure 3.



Number at risk

Group: 0	1338	755	367	194	81	43	26	20
Group: 1	367	207	99	45	25	12	9	8