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Prevalence and predictors of atrial fibrillation type among individuals with recent onset of atrial fibrillation

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Summary

OBJECTIVE: Atrial fibrillation (AF) is considered to be a progressive disease, starting with intermittent episodes that progress over time to more sustained events. However, little is known about the prevalence of and predictors for AF type among patients with recent-onset AF. We aimed to address these issues among a selected population of patients with AF.

METHODS: The Basel atrial fibrillation cohort (BEAT-AF) study is an ongoing prospective multicentre cohort study among patients with AF. At baseline, we obtained information on the date of AF diagnosis, AF type, comorbidities, medication and lifestyle factors. For this analysis, 486 (31.4%) out of 1550 participants with recent-onset AF (defined as AF duration <24 months) were included. Predictors for AF type (non-paroxysmal vs paroxysmal) were obtained using multivariable adjusted logistic regression models.

RESULTS: Mean age was 67 (59–75) years and 136 (28%) were women. Recent-onset paroxysmal AF was observed in 301 (62%) participants, 185 (38%) had non-paroxysmal AF – persistent AF in 148 (30.4%) and permanent AF in 37 (7.6%). In multivariable models, odds ratios for having non-paroxysmal AF around AF diagnosis were 1.03 per year increasing in age (95% confidence interval [CI] 1.01–1.05, p = 0.01); 2.70 (1.5–4.68, p = 0.0004) for history of heart failure; 3.82 (1.05–13.87, p = 0.04) for a history of hyperthyroidism and 1.04 (1.02–1.05, p <0.0001) per beat increase in heart rate.

CONCLUSION: We found a substantial proportion of AF patients with the non-paroxysmal form shortly after diagnosis. Predictors for non-paroxysmal AF were increasing age, history of heart failure or hyperthyroidism, and a higher heart rate.

Keywords: *atrial fibrillation, epidemiology, recent onset*

Introduction

Atrial fibrillation (AF) is a key public health priority, given its high prevalence [1] and its strong association with cardiovascular morbidity and mortality [2]. From a clinical perspective, AF is classified as paroxysmal, persistent or permanent [3, 4]. This classification is important, as several studies have shown that patients with more sustained AF episodes have worse clinical outcomes, and implementation of rhythm control strategies is much more difficult among them [5–7].

AF is currently considered to be a dynamic disease, such that patients are supposed to progress from short self-terminating episodes of AF to the more sustained forms [3]. Experimental studies [8, 9] provide a solid background for the concept of AF progression over time, but clinical studies on this issue are sparse and do not provide a uniform answer. For example, small studies following patients with paroxysmal AF over a long time period have shown that the majority of patients will remain in paroxysmal AF [10, 11]. Other studies with relatively short follow-up suggested a slow but steady progression from paroxysmal to permanent AF [12].

In addition, even less evidence is available on the presenting AF type among patients with new-onset AF. Thus, the prevalence of AF patients who directly present with more sustained episodes and its potential clinical correlates are

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relatively unknown. A better understanding of this issue may help to improve our pathophysiological understanding of human AF and potentially improve prevention and treatment of the disease and its complications.

We therefore assessed the prevalence of AF type in a large unselected cohort of patients with recent-onset AF and evaluated independent clinical predictors for sustained AF in multivariable regression analyses.

Materials and methods

The Basel atrial fibrillation (BEAT-AF) cohort is a prospective multicentre cohort study. Between January 2010 and April 2014, 1550 patients with AF documented on an electrocardiogram (ECG) across seven centres in Switzerland were asked to participate. The inclusion was independent of the duration of AF. Patients were recruited from in- and outpatient clinics. We strongly encouraged all centres to comprehensively screen patients in in- and outpatient clinics and to include consecutive AF patients. The enrolment of patients with acute illnesses was postponed until their health status had stabilised. There were no major exclusion criteria to participation in BEAT-AF. The local ethics committees approved the study protocol and all participants provided written informed consent. Of 1550 included participants, 486 (31.4%) individuals with AF duration <24 months at study entry were included in the current analysis.

Assessment of study variables

Baseline examination included a standardised assessment of personal, medical, lifestyle and nutritional factors by questionnaire (appendix 1, available in a separate file).

Smoking status of the participants was self-reported and classified as current, former, or never smoking. Body mass index (BMI) was calculated by dividing weight in kilograms by height in meters squared. Blood pressure was obtained in duplicate in a quiet environment after at least 5 minutes of rest in a sitting position and a validated device was used. Patients were classified as hypertensive if they reported a history of hypertension or if the mean blood pressure was ≥140 mm Hg or ≥90 mm Hg for systolic or diastolic blood pressure, respectively. Estimated glomerular filtration rate (eGFR) was calculated by applying the Cockcroft-Gault equation to locally measured serum creatinine levels [13]. Plasma levels of brain natriuretic peptide (BNP) were also locally measured. Educational level was self-reported and classified as primary, high school or college/university. The individual physical activity questionnaire (IPAQ) was used for the evaluation of the subjects' physical activity, and at least moderate physical activity was defined as performing ≥150 min of moderate or ≥75 min of intensive physical activity per week [14, 15]. Daily alcohol intake was self-reported and moderate alcohol intake was defined as ≤2 drinks per day for men and ≤1 drink per day for women [14, 15]. A 12-lead ECG was obtained under standardised conditions in every participant. From each ECG, we obtained heart rate and calculated the Sokolow-Lyon index (SLI) as described previously [16]. Left ventricular hypertrophy (LVH) was defined as an SLI >3.5 mV.

Outcome variable

AF subtypes were defined according to current guidelines [3]. Paroxysmal AF was defined as AF that terminates spontaneously within 7 days of onset. Persistent AF was defined as AF that was sustained for more than 7 days or required cardioversion. Permanent AF was recorded if restoration of sinus rhythm was not possible or not further attempted. As the main aim of this study was to assess self-terminating versus non-self-terminating AF, we dichotomised the study sample into paroxysmal or non-paroxysmal AF.

Statistical analysis

Baseline characteristics were grouped according to the presence or absence of paroxysmal AF. Distribution of continuous variables was assessed using skewness, kurtosis and visual inspection of the histogram. Baseline characteristics of continuous variables were presented as means (standard deviation) or medians (interquartile range) and compared using analysis of variance or Kruskal-Wallis tests, as appropriate. Categorical variables were presented as counts (percentages) and compared using chi-squared tests.

Univariable logistic regression models to obtain predictors for the presence of non-paroxysmal AF were performed among a predefined list of covariates, including age, sex, educational level, heart failure, hypertension, diabetes mellitus, stroke, coronary artery disease, hyperthyroidism, LVH, heart rate, BMI, smoking status, physical activity and alcohol consumption. We then built multivariable logistic regression models to obtain independent predictors for the presence of non-paroxysmal AF.

To test the robustness of our results, we then performed three predefined sensitivity analyses. First, we additionally adjusted our multivariable model for plasma levels of BNP and eGFR, which were available in 394 (81.1%) participants. Second, to assess whether the definition of recent-onset AF influences our results, we restricted our patient sample to those 338 patients who had AF onset within 12 months of the baseline visit, and constructed our main multivariable model in this patient population. Third, patients with sustained forms of AF might have higher heart rates, such that heart rate may be a proxy for the outcome variable. In order to avoid this potential issue, we repeated our main analysis without heart rate.

Categorical variables were introduced in all multivariable models using binary indicator variables. We used the SAS statistical software version 9.4 (SAS Institute Inc., Cary, NC, USA) for all analyses. A p-value of <0.05 was prespecified to indicate statistical significance.

Results

Baseline characteristics

Baseline characteristics of the study participants are presented in table 1. Individuals with paroxysmal AF at baseline were younger than those with non-paroxysmal AF (66 vs 70 years, p = 0.009). Participants with non-paroxysmal AF had a significantly higher prevalence of heart failure (25.8 vs 11.3%, p <0001) and hypertension (77.4 vs 69.1%, p = 0.046). BMI, heart rate and diastolic blood pressure were higher among non-paroxysmal AF patients (27.9 ±

4.8 vs 26.9 ± 4.6 kg/m^2, p = 0.02; 77 ± 19 vs 67 ± 17 bpm, p <0.0001 and 81 ± 13 vs 78 ± 12 mm Hg, p = 0.02, respectively).

Predictors of paroxysmal AF presentation

Out of 486 individuals with recent-onset AF, 301 (62%) had paroxysmal AF, 148 (30.4%) had persistent AF and 37 (7.6%) had permanent AF. Results of the regression models are presented in table 2. In multivariable models, significant predictors for recent-onset non-paroxysmal AF were increasing age (odds ratio [OR] per 1 year increase 1.03, 95% confidence interval [CI] 1.01–1.05; p = 0.01), history of heart failure (OR 2.70, 95% CI 1.56–4.68; p = 0.0004), history of hyperthyroidism (OR 3.82, 95% CI 1.05–13.87; p = 0.04) and higher heart rate (OR per 1 beat increase 1.04, 95% CI 1.02–1.05; p <0.0001). Excluding heart rate from the model did not materially alter the results for the other predictors (table 2).

Including BNP and eGFR in the multivariable analyses including those for whom these measures were available did not significantly change our results, with the exception of female sex, which became a significant inverse predictor (OR 0.43, 95% CI 0.23–0.79; p = 0.01), as shown in table 3. BNP but not eGFR was significantly associated with non-paroxysmal AF (OR 2.17, 95% CI 1.62–2.92; p <0.0001). Similar results were also obtained when we limited our analysis to the 338 individuals (n = 215 for paroxysmal AF and n = 123 for non-paroxysmal) with an AF duration <12 months (table 4).

Table 1: Baseline characteristics of study participants.

	Paroxysmal (n = 301)	Non-paroxysmal (n = 185)	p-value
Age (years)	66 (58–74)	70 (61–76)	0.009
Sex (% women)	86 (28.6)	49 (26.3)	0.59
Low educational level	39 (12.9)	32 (17.2)	0.20
History of heart failure	34 (11.3)	48 (25.8)	<0.0001
Hypertension	208 (69.1)	144 (77.4)	0.046
History of diabetes	36 (12.0)	21 (11.3)	0.82
History of stroke	36 (12.0)	26 (14.0)	0.52
History of CAD	58 (19.3)	36 (19.4)	0.98
History of hyperthyroidism	5 (1.7)	8 (4.3)	0.08
LVH	7 (2.33)	2 (1.08)	0.32
Heart rate (beats/min)	67 ± 17	77 ± 19	<0.0001
Systolic BP (mm Hg)	135 ± 18	135 ± 19	0.85
Diastolic BP (mm Hg)	78 ± 12	81 ± 13	0.02
BMI (kg/m^2)	26.9 ± 4.6	27.9 ± 4.8	0.02
BMI <25 kg/m^2	116 (69.1)	52 (31)	0.02
Current smoking	29 (9.7)	21 (11.4)	0.57
At least moderate physical activity	99 (32.9)	57 (30.7)	0.61
Moderate alcohol intake	258 (85.7)	156 (83.9)	0.58

BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; LVH = left ventricular hypertrophy Baseline characteristics of continuous variables are presented as mean ± standard deviation or median (interquartile range). .

Table 2: Predictors for recent-onset non-paroxysmal atrial fibrillation.

Predictor of interest	Univariable model (n = 486)		Multivariable model (n = 476)		Multivariable model* (n = 478)	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	1.02 (1.01–1.04)	0.01	1.03 (1.01–1.05)	0.01	1.03 (1.01–1.05)	0.006
Sex (women)	0.90 (0.60–1.36)	0.62	0.71 (0.43–1.15)	0.16	0.73 (0.46–1.18)	0.20
Low educational level	1.41 (0.85–2.34)	0.19	1.26 (0.70–2.24)	0.44	1.25 (0.71–2.19)	0.44
History of heart failure	2.75 (1.69–4.47)	<0.0001	2.70 (1.56–4.68)	0.0004	2.81 (1.66–4.77)	0.0001
Hypertension	1.52 (0.998–2.32)	0.05	1.11 (0.67–1.85)	0.69	1.16 (0.71–1.90)	0.56
History of diabetes	0.94 (0.53–1.67)	0.84	0.79 (0.40–1.54)	0.48	0.74 (0.39–1.42)	0.37
History of stroke	1.15 (0.67–1.99)	0.62	0.87 (0.47–1.60)	0.66	0.91 (0.51–1.63)	0.76
CAD	0.98 (0.61–1.56)	0.92	0.61 (0.34–1.08)	0.09	0.60 (0.35–1.05)	0.07
History of hyperthyroidism	2.69 (0.87–8.35)	0.08	3.82 (1.05–13.87)	0.04	4.04 (1.13–14.49)	0.03
LVH (electrocardiographic)	0.46 (0.09–2.23)	0.33	0.82 (0.15–4.42)	0.81	0.61 (0.12–3.20)	0.56
Heart rate	1.04 (1.02–1.05)	<0.0001	1.03 (1.02–1.05)	<0.0001	–	–
BMI	1.05 (1.01–1.09)	0.02	1.04 (0.99–1.09)	0.11	1.04 (0.999–1.09)	0.06
Current smoking	1.20 (0.66–2.17)	0.56	1.21 (0.63–2.34)	0.58	1.45 (0.77–2.75)	0.25
At least moderate physical activity	0.91 (0.61–1.35)	0.63	1.03 (0.66–1.59)	0.91	1.06 (0.69–1.61)	0.80
Moderate alcohol intake	0.86 (0.52–1.43)	0.56	1.01 (0.57–1.77)	0.98	1.02 (0.59–1.76)	0.94

BMI = body mass index; CAD = coronary artery disease; CI = confidence interval; LVH = left ventricular hypertrophy; OR = odds ratio * Excluding heart rate

Discussion

Among patients with recent-onset AF, a total of 38% presented with non-paroxysmal AF within 2 years after AF diagnosis. This indicates that an important proportion of individuals have sustained AF forms early after their first diagnosis. In these patients, persistent or permanent AF might indeed be the first clinical manifestation the arrhythmia. Although these patients may have had asymptomatic non-sustained episodes before AF was clinically diagnosed, this study nevertheless raises the possibility that the natural history of AF as currently proposed may not be valid for all patients [3]. This is also true for the opposite finding in earlier studies, namely that many patients with paroxysmal AF do not progress over time [10, 11]. Due to its clinical implications on prognosis and treatment strategies [5–7], a better understanding of the mechanisms associated with AF type at diagnosis and AF progression in general is urgently needed.

To our knowledge, this is one of the first studies to identify independent predictors for the presentation of paroxysmal versus non-paroxysmal AF among men and women with recent-onset AF. In our study, elderly participants, those who had a history of heart failure or hyperthyroidism and those with a faster heart rate were prone to have non-paroxysmal forms of AF within the first 2 years after diagnosis. The importance of structural heart disease for the presence of sustained AF is underscored by our finding that BNP levels were independently associated with the presence of non-paroxysmal AF.

In a previous study that was limited to women [17], age was preferentially associated with the early development of non-paroxysmal forms of AF, which is in line with our findings. However, unlike the results of above-mentioned study, BMI had no predictive value for the presentation of non-paroxysmal forms of AF in our analysis. Median BMI reported by Sandhu et al. was similar to that of our female

Table 3: Predictors for recent-onset paroxysmal atrial fibrillation including laboratory parameters.

Predictor of interest	Multivariable model (n = 394)	
	OR (95% CI)	p-value
Age	0.99 (0.96–1.02)	0.44
Sex (women)	0.43 (0.23–0.79)	0.01
Low educational level	1.57 (0.77–3.20)	0.22
History of heart failure	1.80 (0.94–3.46)	0.08
Hypertension	1.06 (0.57–1.96)	0.85
History of diabetes	0.78 (0.36–1.70)	0.53
History of stroke	1.17 (0.58–2.39)	0.66
CAD	0.52 (0.26–1.03)	0.06
History of hyperthyroidism	4.27 (1.11–16.46)	0.03
LVH (electrocardiographic)	0.96 (0.14–6.70)	0.97
Heart rate	1.03 (1.02–1.01)	<0.0001
eGFR	1.00 (0.99–1.01)	0.48
log BNP*	2.17 (1.62–2.92)	<0.0001
BMI	1.04 (0.98–1.10)	0.22
Current smoking	1.17 (0.55–2.50)	0.69
At least moderate physical activity	1.35 (0.81–2.25)	0.25
Moderate alcohol intake	1.22 (0.62–2.38)	0.56

BMI = body mass index; BNP = brain natriuretic peptide; CAD = coronary artery disease; CI = confidence interval; eGFR = estimated glomerular filtration rate; LVH = left ventricular hypertrophy; OR = odds ratio * BNP was log transformed.

Table 4: Predictors for recent-onset paroxysmal atrial fibrillation defined as new onset within 12 months.

Predictor of interest	Multivariable model (n = 338)	
	OR (95% CI)	p-value
Age	1.04 (1.01–1.07)	0.002
Sex (women)	0.74 (0.41–1.34)	0.32
Low educational level	0.82 (0.40–1.69)	0.59
History of heart failure	1.74 (0.91–3.35)	0.10
Hypertension	0.96 (0.52–1.78)	0.90
History of diabetes	0.99 (0.45–2.17)	0.98
History of stroke	0.71 (0.33–1.54)	0.39
CAD	0.64 (0.32–1.28)	0.21
History of hyperthyroidism	7.54 (1.36–41.68)	0.02
LVH (electrocardiographic)*	–	–
Heart rate	1.03 (1.02–1.05)	<0.0001
BMI	1.03 (0.97–1.08)	0.37
Current smoking	1.62 (0.71–3.67)	0.25
At least moderate physical activity	1.13 (0.66–1.93)	0.67
Moderate alcohol intake	0.98 (0.50–1.95)	0.96

BMI = body mass index; CAD = coronary artery disease; CI = confidence interval; LVH = left ventricular hypertrophy; OR = odds ratio * Correction for LVH not possible (n = 0 and n = 6 among non-paroxysmal and paroxysmal atrial fibrillation, respectively; p-value for difference = 0.06)

population. However, when compared with our study, there was a lower prevalence of females with a normal BMI (<25 kg/m^2) and of females with a higher one (≥30 kg/m^2) among both paroxysmal and non-paroxysmal AF groups in the earlier study. Therefore, differences regarding obesity prevalence between Americans and Europeans might explain these discrepancies.

Age [5, 10, 12, 18], BMI [19], underlying heart disease [5, 12, 18], hypertension [5, 12, 20], DM [20], history of coronary artery disease [18] or stroke [5], chronic obstructive pulmonary disease [5] and heart rate independent of rhythm [20] had previously been identified as risk factors for the progression of AF. However, the majority of these studies were in patients with established paroxysmal AF, so that a distinction between rapid progression in patients with recent-onset of AF and slow but steady progression in the course of AF has not been made. Results regarding BMI, diabetes, history of coronary artery disease and hypertension differed between the above-mentioned previous studies and our results. These differences raise the possibility that there are different subtypes of AF with different speeds of progression.

Among others, increasing age, hyperthyroidism, hypertension, heart failure, diabetes, coronary artery disease, obesity, smoking, exercise and alcohol consumption have already been reported to be risk factors for the new onset of AF [21–30]. In our study, however, only the first three seemed to be related to the presentation of non-paroxysmal forms of AF shortly after diagnosis. As previously reported [5, 10, 12, 18], classical cardiovascular conditions such as hypertension, diabetes, history of stroke or coronary artery disease, or overweight seem to be responsible for a steady progression of AF over time, possibly in parallel with the progression of the structural heart disease. Interestingly, these classical risk factors seem to be less important for the definition of AF type at diagnosis. We found that other factors such as hyperthyroidism, heart rate or structural heart disease might be responsible for the morphological and/or electrophysiological substrate facilitating the presence of sustained AF early in the disease process. Because of its therapeutic and prognostic implications, this might be of major relevance for the management of patients with AF and further investigations are needed.

Strengths and limitations

A major strength of our study is the availability of a large and well-characterised cohort of individuals with AF. Limitations that need to be taken into account when interpreting our results are the following: first, the cross-sectional design of this study does not allow causal inferences; second, the low prevalence of hyperthyroidism means that the results involving this parameter should be interpreted cautiously; third, imaging data were not available for this analysis, but we were able to quantify BNP levels in the majority of participants as a surrogate for structural and/or functional changes of the heart.

Conclusion

This is one of the first studies to present the prevalence of and predictors for non-paroxysmal AF among patients with recent-onset AF. Among 486 individuals with recent-onset AF, a total of 185 (38%) presented with the non-paroxysmal form. Thus, our data suggest that a substantial proportion of AF patients have non-paroxysmal AF shortly after diagnosis. Predictors of recent onset non-paroxysmal AF were increasing age, history of heart failure and hyperthyroidism as well as a higher heart rate. More studies are needed to understand which patients directly present with non-paroxysmal AF and what the clinical significance of this phenomenon is.

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Potential competing interests

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Appendix 1

Baseline questionnaire

The questionnaire is available as a separate file for downloading at https://smw.ch/en/article/doi/smw.2018.14652/.