Towards improved risk prediction of incident atrial fibrillation and progression of atrial fibrillation

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Part 3

Risk markers for progression of atrial fibrillation

Chapter 5

Atrial fibrillation progression and outcome in patients with young onset atrial fibrillation.

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ABSTRACT.

Aims. Clinicians increasingly encounter patients with young-onset atrial fibrillation (AF). Aim is to study clinical profile, AF progression and outcome of patients with young-onset AF.

Methods and results: A total of 468 patients with paroxysmal or persistent AF starting <60 years of age were included. Clinical profile, AF progression, defined as development of permanent AF, and cardiovascular events were prospectively collected. Onset of AF was at 46±10 years, 354 (76%) were men, 329 (70%) had paroxysmal AF, 50 (11%) had AF without risk factors or comorbidities and 118 (25%) had familial AF. Hypertension was present in 207 (44%), heart failure in 44 (9%). During 7.2 (2.7-10.0) years, 56 (11%) had AF progression (2.0%/year). Progression rate in patients receiving antiarrhythmic drugs or pulmonary vein isolation during follow-up was not different from patients who did not. Multivariable determinants of AF progression included diastolic blood pressure (HR 1.031 [(95% CI 1.007-1.055], p=0.010) and left atrial size (HR 1.055 [1.012-1.099], p=0.012). Cardiovascular events occurred in 61 patients (13%; 2.4%/year). Multivariable determinants of cardiovascular events were PR interval (HR 1.015 [1.005-1.024], p=0.002) and left ventricular hypertrophy (HR 3.429 [1.712-6.868], p=0.001). Yearly event rate was higher in patients who had developed AF progression, compared to patients without progression (4.9 [2.3-9.0]% vs. 1.9 [1.4-2.6]%, p=0.006).

Conclusion. Nine out of 10 patients with young-onset AF had risk factors and comorbidities, 25% had familial AF. AF progression to permanent AF and cardiovascular events occurred in 2.0% and 2.4% per year, respectively. Cardiovascular events increased after AF progression had occurred.

Key words: atrial fibrillation; young-onset; atrial fibrillation progression; cardiovascular outcome

CONDENSED ABSTRACT.

Of the total of 468 patients with young-onset AF, 9 out of 10 had risk factors and comorbidities, 25% had familial AF. AF progression to permanent AF and cardiovascular events occurred in 2.0% and 2.4% per year, respectively. Cardiovascular events increased after AF progression had occurred.

What's new?

- Most patients with young-onset AF had AF in the setting of comorbidities and AF risk factors. Only 11% had AF without known comorbidities or risk factors;
- Long term AF progression rate to permanent AF was low with 2.0% a year;
- Long term prognosis was good with an yearly cardiovascular event rate of 2.4%;
- Event rates were higher after AF had progressed to permanent AF.

INTRODUCTION

Atrial fibrillation (AF) often occurs at an older age, and most commonly in the presence of concomitant cardiovascular risk factors or diseases.(1) Yet, AF incidence at young age is increasing.(2) This may relate to changes in life-style, including consumption pattern, obesity and lack of physical activity, which may lead to earlier development of cardiovascular risk factors and comorbidities.(2,3) The relative contribution of heritability may also be of greater importance in younger individuals.(1) Data on the exact clinical phenotype of young-onset AF, however, is sparse.(3) The general notion often is that many young-onset AF patients have AF without comorbidities, i.e. AF occurring in the absence of AF risk factors, but also that data is sparse.(4)

AF frequently emerges as a progressive disease that starts off as simple, paroxysmal self-terminating AF and eventually progresses to persistent and permanent non-self-terminating AF. Underlying clinical and subclinical diseases guide the process of ongoing structural atrial remodeling and thus progression of AF. Atrial remodeling is thought to start years before the first AF episode.(5) Yearly progression rates that have been reported vary between <1% to >30%, depending on the severity of underlying cardiovascular diseases, and AF progression definition.(6) AF progression is of clinical importance because it has been associated with worse cardiovascular outcome.(7-9) Therefore, it is of importance to predict the patients at risk for AF progression. Current risk-stratification for AF progression is limited. Even less is known on AF progression in young patients.

In the present single-center, observational study we aim to describe the clinical profile, AF progression to permanent AF, and cardiovascular outcome of patients with young-onset paroxysmal and persistent AF.

METHODS

Study population. The Phenotyping Young-Onset Atrial Fibrillation Patients study (YOUNG AF) is a prospective, single-center, observational study that was performed at the University Medical Center Groningen, The Netherlands. A total of 500 patients were included between August 2012 and December 2013. The institutional review board approved the study protocol, and all patients provided written informed consent. At the outpatient clinic patients with AF onset <60 years, who were at least 18 years at time of inclusion were asked to participate. Patients with post-operative AF, myocardial infarction or acute coronary syndrome <1 month prior to onset of AF were non-eligible. Also, patients with AF due to another acute trigger (e.g. infection) and patients with hyperthy-

roidism <3 months before AF onset were non-eligible. In total, 3 patients were excluded because not meeting the inclusion criteria (1 hyperthyroidism <3 months before AF onset, 2 aged >60 years at AF onset). Of the 497 patients, no follow-up data was available of 9 patients and 20 had permanent AF at baseline. All analyses were performed using the remaining 468 patients. Data regarding clinical profile was collected closest to the moment of the diagnosis of AF (index-visit). Information regarding family history, cardiovascular risk factors and diseases, life style-related risk factors for AF, physical examination, 12-lead electrocardiogram, laboratory analyses, and echocardiography was also collected prospectively. The follow-up frequency and follow-up investigations, after the index-visit, were led to the discretion of the treating physician. In the majority at least yearly follow-up visits were planned. Information regarding these visits was collected from the electronic medical records.

Definitions. AF progression was defined as development of permanent AF (i.e. sinus rhythm that cannot be restored or is no longer pursued by the treating physician). Type of AF was defined according to the 2016 European Society of Cardiology AF guidelines into paroxysmal (<7 consecutive days of AF), persistent (>7 consecutive days of AF) and permanent AF.(1) Heart failure was defined as the presence of signs or symptoms associated with heart failure (New York Heart Association functional class II or III), previous hospitalization for heart failure or left ventricle ejection fraction (LVEF) ≤45% as assessed by echocardiography or any other imaging modality. Left ventricular hypertrophy (LVH) was classified using echocardiographic left ventricular mass index (LVMI) >95 g/m^2 in women and >115 g/m^2 in men. Hypertension was defined as systolic blood pressure >140mmHg, diastolic blood pressure >90mmHg, or by use of medication prescribed for hypertension. Coronary heart disease was defined as a history of myocardial infarction, percutaneous coronary intervention or coronary artery bypass grafting. Peripheral artery disease was defined on the basis of a clinical diagnosis by a vascular specialist or observed with Doppler ultrasonography or other imaging modality. Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease formula. Chronic kidney disease was defined as an eGRF <60 mL/min. Body mass index (BMI) was calculated by dividing weight to height squared (kg/m^2). Obesity was defined as BMI >30 kg/m^2. Familial AF was defined as a history of AF <60 years in ≥1 first-degree family members. AF without comorbidities was diagnosed in the absence of congenital heart disease, cardiomyopathies, hypertension, coronary artery disease, peripheral artery disease, pulmonary diseases, heart failure, diabetes mellitus, chronic kidney disease, obesity, LVH, diastolic dysfunction (e'<8 cm/sec and/or lateral e'<10 cm/sec), moderate or severe valvular disease, subclinical hypertension (systolic blood pressure >130-140 mmHg or diastolic blood pressure >80-90 mmHg), smoking, excessive sports practice and excessive alcohol use. The stroke risk-score CHA_2DS_2-VASc

was calculated by counting points for congestive heart failure, hypertension, age >75 years (2 points), diabetes mellitus, stroke or transient ischemic attack (TIA; 2 points), vascular disease, age 65-74 years and female sex. The HATCH score, an AF progression score, was calculated by counting points for hypertension, age >75 years, stroke or TIA (2 points), chronic obstructive pulmonary disease and heart failure (2 points).

Follow-up. We used electronic medical records to obtain information on development of AF progression and cardiovascular events. Rhythm control including atrial ablation was first choice therapy.(1) During follow-up data on AF therapies was collected, including use of class I and III anti-arrhythmic drugs (AAD) and atrial ablation. Cardiovascular events included cardiovascular death and heart transplantation, 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 (ICD). Cardiovascular death was defined as death occurring due to any cardiovascular disease. Stroke was defined as the sudden onset of a focal deficit with permanent damage and categorized as either ischemic (occlusion of a major cerebral artery documented by means of imaging) or hemorrhagic. Systemic embolism was defined as an acute vascular occlusion of an extremity or organ documented by any imaging modality, operative report or autopsy report. Major bleeding was defined as a reduction in the hemoglobin level by more than 2g/dL, requiring transfusion of ≥2 units of blood or symptomatic bleeding in a critical area or organ necessitating hospitalization. Syncope was defined as a transient loss of consciousness potentially to be caused by a rhythm disorder. Life-threatening adverse effects of AF drugs included conduction disturbances and ventricular arrhythmias necessitating hospitalization. Sustained ventricular tachycardia was defined as ventricular tachycardia lasting >30 seconds or necessitating termination by electrical cardioversion because of hemodynamic instability. Cardiac arrest was defined as circulatory arrest necessitating resuscitation and hospitalization. Follow-up started at index-visit and was continued until February 2016 with a maximum of 10 years, or until death.

Statistical analysis. Descriptive statistics of the total population, and subgroups with and without AF progression, were presented as mean±standard deviation or median (interquartile range [IQR]) for continuous variables, depending on normality of the data. Categorical variables are presented as numbers with percentages. Yearly event rates were calculated by dividing the number of follow-up years by the number of events, with censoring post first event. Additionally, repeated events analyses were performed as well. In an individual patient differences in event rates and 95% confidence interval (CI) were calculated by the incidence rate comparison tool using MedCalc for Windows version 17.6. Differences in patient characteristics between patients with and without AF progression were evaluated using Fisher's exact test (2 categories) and Chi-square test (>2 categories)

for categorical data, and the student's T-test and Mann-Whitney-U test for continuous data, depending on the normality of the data. Univariable Cox proportional hazard regression was used to find determinants of AF progression and cardiovascular outcome. Results are given as hazard ratios (HR) with 95% CI. All covariates with a P<0.1, excluding those with significant correlations with other covariates, were used to create a stepwise multivariable Cox proportional hazard regression model. Only statistically significant (P<0.05) remained in the final model. As secondary analyses, we additionally adjusted the multivariable model for sex and treatment during follow-up. Variables included in the final regression model were tested for significant interactions. The proportionality hazards assumption was evaluated by testing the correlation coefficient between survival time and the scaled Schoenfeld residuals. A P-value <0.05 was considered statistically significant. Kaplan Meier curves were created to illustrate the course of AF progression and cardiovascular events during follow-up. Statistical analyses were performed using IBM SPSS Statistics version 23.0 (Armonk, NY, USA) unless otherwise mentioned.

RESULTS

Clinical characteristics. Table 1 shows the baseline characteristics. Mean age at onset of AF was 46±10 years, and 354 (76%) were men. On average, there was an approximate 3-year difference between the index-visit and AF onset. The majority had paroxysmal AF (329 [70%]). Overall, patients had a low number of comorbidities. A total of 50 (11%) patients had AF without comorbidities. Familial AF was present in 118 (25%). Patients with AF without comorbidities had a higher percentage of familial AF (40% vs. 23%, p=0.015). Despite their low stroke risk, 27 (6%) had a history of stroke or TIA.

Atrial fibrillation progression. During a median follow-up of 7.2 [2.7-10.0] years, 56 (12%) out of 468 patients had AF progression to permanent AF, equivalent to 2.0%/year (**Figure 1-a).** There was no difference in progression rate in patients who underwent pulmonary vein isolation (PVI) or received class I or III AAD during follow-up, compared to patients who did not (26 [10.1%] vs 30 [14.3%], p=0.197). Patients with AF progression were more often men, had persistent AF at the index-visit, valvular disease and heart failure (**Table 1**). Both systolic and diastolic blood pressure were higher in patients with AF progression. Echocardiographic differences included a larger left atrial size and a higher LVMI. The HATCH score was significantly higher in patients with AF progression (HR 1.273 [95% CI 1.024-1.584], p = 0.029). Multivariable determinants of AF progression included diastolic blood pressure (HR 1.031 [95% CI 1.007-1.055], p=0.01) and left atrial size (HR 1.055 [95% CI 1.012-1.099], p=0.012) (**Table 2**). After adjustment for sex and treatment during follow-up, this effect remained present.

Table 1. Patient characteristics at index-visit of total population, with and without AF progression.

	All patients (n=468)	AF progression (n=56)	No AF progression (n=412)	P-value
Age at index-visit (years)	49 ± 9	50 ± 9	49 ± 9	0.41
Age at AF-onset (years)	46 ± 10	47 ± 9	46 ± 10	0.46
Men	354 (76%)	49 (84%)	305 (74%)	0.03
Type of AF				<0.001
Paroxysmal	329 (70%)	25 (45%)	304 (74%)	
Persistent	139 (30%)	31 (55%)	108 (26%)	
Heart failure	44 (9%)	10 (18%)	34 (8%)	0.02
Hypertension	207 (44%)	30 (54%)	177 (43%)	0.21
Diabetes mellitus	21 (5%)	2 (4%)	19 (5%)	0.72
COPD	17 (4%)	1 (2%)	16 (4%)	0.57
Coronary artery disease	45 (10%)	5 (9%)	40 (10%)	0.85
Peripheral artery disease	8 (2%)	2 (4%)	6 (2%)	0.25
Stroke or TIA	27 (6%)	5 (9%)	22 (5%)	0.28
Chronic kidney disease	10 (2%)	2 (4%)	8 (2%)	0.43
Hypercholesterolemia	175 (41%)	26 (50%)	149 (40%)	0.18
History of hyperthyroidism	10 (2%)	2 (4%)	8 (2%)	0.43
AF without comorbidities	50 (11%)	6 (11%)	44 (11%)	1.00
Familial AF	118 (25%)	13 (23%)	105 (26%)	0.87
CHA_2DS_2VASc	1 (0-2)	1 (0-2)	1 (0-2)	0.20
HATCH score	1 (0-1)	1 (0-2)	1 (0-1)	0.04
EHRA symptom class				<0.001
I	39 (9%)	14 (26%)	25 (7%)	
II	325 (74%)	35 (65%)	290 (76%)	
III	69 (16%)	4 (7%)	65 (17%)	
IV	4 (1%)	1 (2%)	3 (1%)	
Physical examination				
Height (cm)	182 ± 10	182 ± 10	182 ± 10	0.99
Weight (kg)	91 ± 17	88 ± 15	92 ± 18	0.08
BMI (kg/m^2)	27 (24-30)	26 (24-28)	27 (24-30)	0.05
Obesity (BMI>30)	86 (26%)	6 (15%)	80 (27%)	0.17
Systolic blood pressure (mmHg)	131 ± 20	136 ± 20	130 ± 20	0.02
Diastolic blood pressure (mmHg)	82 ± 12	86 ± 12	81 ± 11	<0.001
Electrocardiography				
Heart rate (bpm; in sinus rhythm)	65 (57-72)	64 (57-70)	65 (58-73)	0.46
PR interval (ms)	160 (146-176)	165 (157-188)	160 (144-174)	0.05
Echocardiography				
Moderate or severe valve disease	35 (7%)	8 (14%)	27 (7%)	0.04

Table 1. Patient characteristics at index-visit of total population, with and without AF progression. (continued)

	All patients (n=468)	AF progression (n=56)	No AF progression (n=412)	P-value
Left ventricular hypertrophy	50 (11%)	8 (14%)	42 (10%)	0.35
Left ventricular mass index (g/m^2)	80 (69-93)	88 (81-98)	79 (69-92)	0.01
LA volume (mL)	54 (42-68)	60 (50-70)	53 (41-65)	0.02
LA volume index (mL/m^2)	25 (20-31)	28 (24-33)	24 (20-31)	0.07
LA parasternal long axis (mm)	41 ± 6	43 ± 6	40 ± 6	0.002
LVEF (%)	60 (55-60)	60 (50-60)	60 (58-60)	0.05
Laboratory results				
Creatinine (µmol/L)	85 (73-95)	91 (79-102)	84 (72-95)	0.01
eGFR (mL/min)	81 ± 17	76 ± 20	81 ±16	0.27
Total cholesterol (mmol/L)	5.3 ± 1.1	5.0 ± 1.1	5.3 ± 1.1	0.13
HDL cholesterol (mmol/L)	1.2 (1.0-1.4)	1.1 (0.9-1.3)	1.2 (1.0-1.5)	0.23
LDL cholesterol (mmol/L)	3.3 (2.7-4.0)	3.2 (2.4-4.0)	3.3 (2.7-4.0)	0.52

Data is expressed as mean ± standard deviation ± SD, median (IQR) or numbers (%).
Abbreviations: AF=atrial fibrillation; BMI=body mass index; CHA2DS2-VASc=acronym for congestive heart failure, hypertension, age >75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65-74 years and female sex; COPD=Chronic obstructive pulmonary disease; eGFR=estimated glomerular filtration rate; EHRA=European Heart Rhythm Association; HATCH=acronym for hypertension, age >75 years, stroke or transient ischemic attack, chronic obstructive pulmonary disease and heart failure; HDL=high density lipoprotein; ICD=implantable cardiac defibrillator; LA=left atrial; LDL=low density lipoprotein; LVEF=left ventricular ejection fraction; PM=pacemaker; TIA=transient ischemic attack; VF=ventricular fibrillation; VT=ventricular tachycardia.

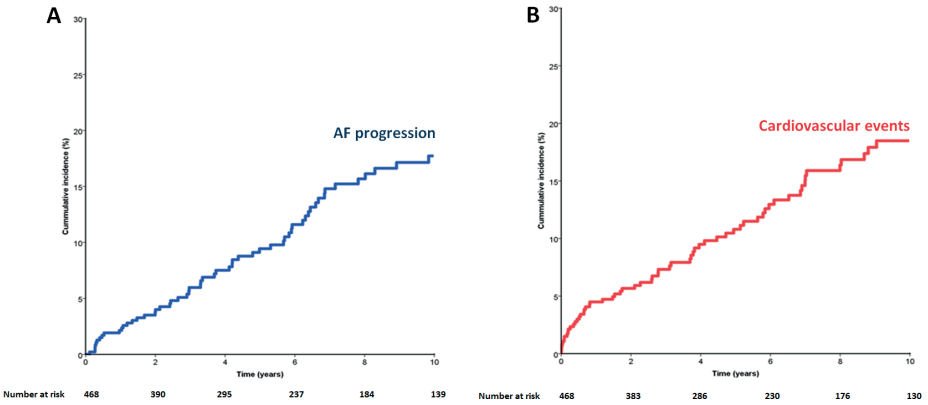

Figure 1 a-b. **A –** Kaplan Meier curve showing the cumulative AF progression rate to permanent AF during follow-up.
B – Kaplan Meier curve illustrating the cumulative incidence of cardiovascular events during follow-up.

Table 2. Univariable and multivariable determinants of AF progression.

	Univariable			Multivariable		
	HR	95% CI	P value	HR	95% CI	P value
Diastolic blood pressure	1.036	1.015-1.058	0.001	1.031	1.007-1.055	0.010
LA parasternal long axis (mm)	1.056	1.014-1.098	0.008	1.055	1.012-1.099	0.012
Creatinine (µmol/L)	1.088	1.001-1.015	0.020			
HATCH	1.273	1.024-1.584	0.029			
PR interval (ms)	1.011	1.000-1.021	0.050			
Heart failure	1.963	0.990-3.891	0.053			
Male	2.580	1.361-4.891	0.081			
LVEF (%)	1.273	1.024-1.584	0.082			
Total cholesterol (mmol/L)	0.794	0.605-1.043	0.097			

Cox proportional hazards regression on determinants associated with AF progression.
Abbreviations: CI=confidence interval; HATCH=acronym for hypertension, age >75 years, stroke or transient ischemic attack, chronic obstructive pulmonary disease and heart failure; HR=hazard ratio; LA=left atrial; LVEF=left ventricular ejection fraction.

Cardiovascular outcome. During 7.2 [2.7-10.0] years of follow-up, 61 (11%; 2.4% per follow-up year) patients had at least 1 cardiovascular event (**Figure 1-b**). A total of 20 patients had >1 event and the total number of events was 90 during follow-up. Including the repeated events, event rate was 3.0% per year.

Patients who developed AF progression had higher yearly cardiovascular event rates (**Table 3**). Sixteen patients with AF progression had a total of 25 events. Ten of those events occurred before AF had progressed to permanent AF. Ten patients had 15 events after progression of AF. After AF progression, patients had a higher event rate (4.9 [2.3-9.0]% vs. 1.9 [1.4-2.6]% a year, p=0.006, **Figure 2**). Including repeated events, this effect remained significant (6.3 [3.5-10.4]% vs. 2.0 [1.5-3.2], p<0.001). AF progression had a HR of 2.222 (1.114-4.430, p=0.023) for cardiovascular events. This effect remained after adjusting for differences in diastolic blood pressure, heart failure, sex and LVH (HR 2.347 [1.109-4.968], p=0.026).

Pacemaker implantation, heart failure hospitalization, syncope and ICD implantation were most frequently observed. A total of 7 (2%) ischemic strokes were observed. Four patients used anticoagulation therapy at the time of stroke, 3 not because a CHA_2DS_2-VASc was 0 or 1. Heart failure hospitalizations and ICD implantations were more common in patients with AF progression. No differences in other individual components were observed.

Table 3. Cardiovascular events in patients after AF progression had occurred (i.e. were in permanent AF) and without AF progression.

	After AF progression (n=56)	No AF progression (n=412)	P-value
Composite endpoint	4.87%/year	1.93%/year	0.006
Endpoint components			
Death from cardiovascular cause or heart transplantation	0.42%/year	0.04%/year	0.039
Heart failure hospitalization	1.79%/year	0.40%/year	0.005
Ischemic stroke	-	0.27%/year	0.419
Systemic embolism	-	-	
Major bleeding	-	0.08%/year	0.667
Syncope	0.86%/year	0.27%/year	0.132
Life-threatening adverse effect of rate- or rhythm-control drugs	-	0.12%/year	0.598
Sustained ventricular tachycardia	0.87%/year	0.24%/year	0.088
Cardiac arrest	0.42%/year	0.16%/year	0.353
ICD implantation	0.86%/year	0.24%/year	0.090
Pacemaker implantation	1.37%/year	0.77%/year	0.352

Data is expressed as yearly event rates. P value is given for the difference between patients after AF progression had occurred (i.e. were in permanent AF) and without AF progression.
Abbreviations: AF=atrial fibrillation; ICD=implantable cardiac defibrillator.

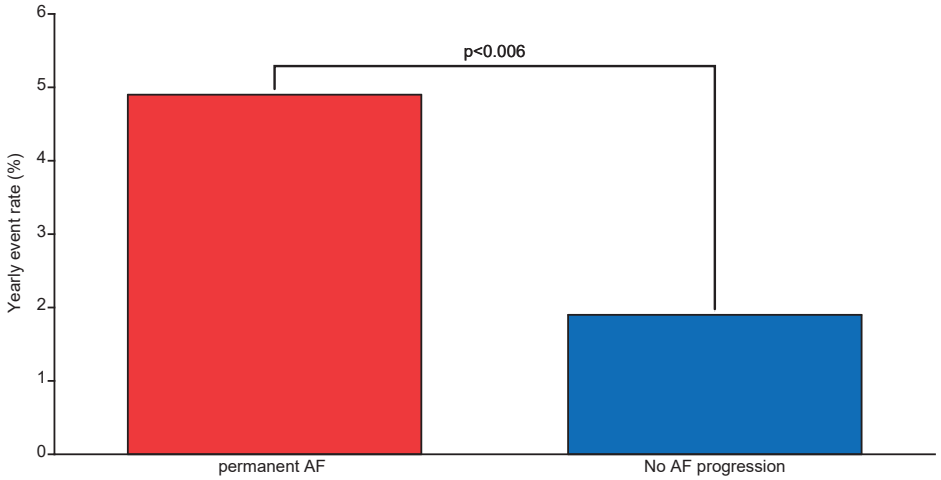

Figure 2. Yearly event rate in patients with permanent AF versus patients without AF progression.

Table 4 shows the univariable and multivariable determinants of cardiovascular outcome. Multivariable determinants included a longer PR interval (HR 1.015 [95% CI 1.005-1.024], p=0.002) and presence of LVH (HR 3.429 [95% CI 1.712-6.868], p=0.001).

Table 4. Univariable and multivariable determinants of cardiovascular events.

	Univariable			Multivariable		
	HR	95% CI	P value	HR	95% CI	P value
PR interval (ms)	1.015	1.006-1.024	0.001	1.015	1.005-1.024	0.002
LVH	2.312	1.277-4.184	0.006	3.429	1.712-6.868	0.001
LVMI (g/m^2)	1.016	1.003-1.029	0.019			
Heart rate (bpm)	0.975	0.949-1.001	0.063			
COPD	2.365	0.857-6.520	0.096			

Cox proportional hazards regression on determinants associated with cardiovascular events during follow-up.
Abbreviations: bpm=beats per minute; CI=confidence interval; COPD=Chronic obstructive pulmonary disease; HR=hazard ratio; LVH=left ventricular hypertrophy; LVMI=left ventricular mass index.

DISCUSSION

The present study shows that 9 out of 10 patients with young-onset AF had risk factors and comorbidities. AF without comorbidities occurred in a minority of patients, but familial AF was present in one out of four. AF progression to permanent AF and cardiovascular events occurred at a low yearly rate. Of importance, the cardiovascular event rate increased after AF progression to permanent AF.

Clinical profile. The clinical profile in the young-onset AF patients was comparable to patients in whom AF started at an older age.(7,9) In the present cohort, patients with young onset AF, however, were more often men compared to older AF cohorts.(7,10) This may be partly explained by electrophysiological differences between pre- and post-menopausal women. Among other factors, protective effects of estrogens on cardiovascular diseases may have accounted for the lower percentage of women with young-onset AF.(11)

Most patients had comorbidities despite their age. Hypertension was most often prevalent. Obesity, considered a more novel risk-factor, was present in one out of four.(2) More and more data become available that identifying and treating risk factors and comorbidities is key in AF treatment, preventing progression of atrial remodeling. This includes subclinical vascular diseases and subclinical hypertension.(1,12) Identifying and implementing these factors in risk-stratification models may improve prognosis in AF patients.

Familial AF was present in 25%, which is consistent with earlier findings that familial AF is a risk factor for developing AF. Its incidence varies widely, ranging from 5 to 46%.(13,14) Weng et al. described the long-term probability of developing AF considering

genetic predisposition.(15) In those within the lowest tertile of genetic predisposition for developing AF, the incidence was 22.3%, compared to 48.2% in patients within the highest tertile. Thus genetics can play a substantial role in AF development , which may play a role in daily practice in the future. For now, the role of genetics in daily AF management is limited and was therefore not included in the analyses.

It is generally believed that many young patients have AF without comorbidities. The prevalence of AF without comorbidities varies between <1% to 68%, depending on type of AF, age of AF onset and lone AF definition. Wyse et al. advocate limiting the use of the term lone AF, since comorbidities are often underdiagnosed and its definition is used inconsistently.(4) Our data shows that only 11% had young-onset AF without a risk-factor or comorbidity, which may still be an overestimation since this definition did not include subclinical vascular diseases. Thorough work-up is needed to identify cardiovascular diseases or risk-factors and treat them accordingly.(1)

Atrial fibrillation progression. During follow-up, our young-onset AF patients showed a progression rate to permanent AF of 2.0% per year. In patients with self-terminating AF the progression rate varies with the population studied and the means and duration of rhythm monitoring and follow-up, ranging from <1% to >30% per year. Potpara et al. examined 242 patients (age 43±10) with newly diagnosed AF without known comorbidities.(16) A 26.9% progression rate was observed during 12.1 years of follow-up, equivalent to yearly AF progression rate of 2.2%, thus comparable to our data.

Treatment during follow-up could potentially influence AF progression. We did not observe any difference in AF progression rate in patients receiving AAD and/or PVI during follow-up, compared to patients who did not.

Multiple clinical factors have been associated with AF progression. De Vos et al. developed the previously mentioned AF progression risk score HATCH.(7) They showed a yearly progression rate of 15% in older patients (mean age 64±13 years). We also could show that the HATCH score was associated with AF progression. Independent factors associated with AF progression in our cohort were diastolic blood pressure and left atrial size. High diastolic blood pressure might indicate inadequate treatment of underlying hypertension, enhancing the atrial remodeling processes and thus enabling the arrhythmia to become permanent. Larger left atrial dimensions are also considered as marker of more advanced atrial remodeling, further contributing to AF progression.(17)

Cardiovascular outcome. We observed a cardiovascular event rate of 2.4%/year. De Vos et al. reported data from the Euro Heart Survey on several major adverse cardio-

vascular events during 1 year follow-up, including a combined event rate of stroke and death of 3%.(7) Our data shows that after progression to permanent AF, the event rate is higher compared to patients without AF progression. We observed a very low yearly stroke and death rate. Camm et al. showed that, in a cohort of over 5000 patients with recent-onset AF (mean age 66±12 years) 18% had a clinical outcome event in 1 year of follow-up – including stroke (2%), and death (3%).(10) Vannasche et al. observed a worse cardiovascular outcome in patients with persistent or permanent AF compared to paroxysmal AF.(9) Our current data shows that this is also the case in young-onset AF patients. After patients had progressed to permanent AF, the event rate was much higher. This could partly be explained by expression of more advanced atrial remodeling due to more severe underlying risk factors and cardiovascular diseases, and the higher burden of AF itself. After adjusting for differences in some characteristics, AF progression itself remained significantly associated with cardiovascular events. However, whether AF progression is just a marker of more severe underlying cardiovascular disease, or also a cause cannot be concluded form our data. PR interval and LVH assessed by echocardiography were associated with cardiovascular events, both being markers of severity of associated diseases and cardiac remodeling. The relation of AF and PR interval is well known and a longer PR interval has been associated with adverse events, i.e. pacemaker implantations, thromboembolism and mortality(18) LVH can be considered a result of increased workload of the left ventricle due to several underlying conditions, and has been associated with cardiovascular morbidity and mortality.(19) One could hypothesize that the association of LVH and cardiovascular events may be due to diastolic dysfunction that is highly prevalent in these patients, resulting in heart failure with a preserved ejection fraction.(20)

Study strengths and limitations. Strengths of present study include the well characterized cohort and the unique large young onset AF population. Associations that have been found do not necessarily reflect a cause-effect relationships, which may be considered a limitation. Treatment of AF was led to the discretion of the treating physician, which may have influenced our final results. We did not implement dynamic risk profiling in our analyses. Sleep apnea syndrome was not routinely screened for and was therefore not included in our analyses.

Conclusion. The present study demonstrates that the large majority of patients with young-onset AF had AF in the setting of risk factors. One in four had familial AF. Yearly event rates for AF progression and cardiovascular events in these patients were low. Patients with AF progression had a higher yearly event rate compared to patients without AF progression in our study population.

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