

# Evolution of Paroxysmal Atrial Fibrillation to Persistent or Permanent Atrial Fibrillation: Predictors of Progression

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## Abstract

**Introduction:** Paroxysmal atrial fibrillation (PAF) eventually progresses to persistent and permanent AF. The predictors of progression from PAF to persistent and permanent AF are poorly understood.

**Methods:** Electronic medical records of 437 patients with PAF were reviewed in a retrospective cohort study. Patients were followed in time and progression to persistent/permanent AF was recorded. Demographic, clinical and echocardiographic information was collected. A logistic regression analysis was performed to identify predictors of progression to persistent/permanent AF.

**Results:** Over a mean duration of  $57.3 \pm 55.9$  months, 32.4% of patients progressed to persistent/permanent AF. Mean age of the population was  $67.9 \pm 13.4$  years with 57% males and 92% Caucasian. Univariate analysis identified higher body mass index (BMI), cardiomyopathy, diabetes, valvular heart disease (VHD), larger left atrial size (LA) and higher pulmonary artery pressure as predictors of progression. Multivariate logistic regression analysis larger left atrial size (OR 1.46, CI 1.05-2.04, P 0.002), cardiomyopathy (OR 2, CI 1.1- 3.3, P 0.003), and moderate to severe valvular heart disease (OR 3.3, CI 1.4-5, P 0.008) as significant predictors of progression to persistent/permanent AF.

**Conclusions:** Our study shows that PAF patients with larger LA, valvular heart disease and cardiomyopathy predict progression of PAF to persistent/permanent AF. Higher BMI and cardiomyopathy predicted progression to persistent AF while larger LA size and VHD predicted progression to permanent AF.

## Introduction

Atrial fibrillation (AF) is the most common arrhythmia in the world and is associated with significant morbidity and mortality. AF increases the risk for stroke, heart failure and mortality.<sup>1-3</sup> Incidence and prevalence of AF increases with age and the risk doubles with each advancing decade.<sup>4-6</sup> While there are 2.3 million people with AF currently, it is estimated that the prevalence of AF increases to 6 million by year 2050 in the United States alone.<sup>7</sup>

AF frequently starts as paroxysmal atrial fibrillation (PAF) and gradually progresses to permanent atrial fibrillation in about 77% of patients over a time period of 14 years despite anti-arrhythmic therapy as shown in a study by Kato et al.<sup>8</sup> Epidemiological studies and animal models suggest that AF begets AF since the fibrillating myocardium causes electrical remodelling that further perpetuates AF.<sup>9,10</sup> Diabetes, hypertension, heart failure, obesity, obstructive sleep apnea, myocardial infarction and valvular diseases are some of the known risk factors for AF.<sup>4, 11-15</sup> However, the factors that

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cause progression of AF from paroxysmal to persistent and permanent AF are poorly understood.

The NHLBI workshop recently indicated that secondary prevention of AF is the most feasible strategy to prevent AF.<sup>16</sup> For this however, it is necessary to understand the factors that cause recurrent AF as well as its progression. Identifying the factors that cause progression of AF would identify targets for secondary prevention. While some older studies have identified factors of progression from PAF to chronic AF there are very few studies which specifically looked at predictors of progression to persistent and permanent AF separately.

In this study we attempted to identify those clinical, echocardiographic and treatment variables that might influence the progression of AF from a paroxysmal type to a persistent and permanent form.

## Methods

A retrospective study was conducted at a large academic center (University of Kansas Hospitals, Kansas City, KS) and electronic medical records were reviewed. All patients with PAF diagnosed at any time point between 1999 and 2007 and followed in the cardiology clinics were included. Patients whose initial diagnosis was persistent or permanent AF were excluded.

Patients with PAF were followed over time until April 2009 and records at every clinical encounter were reviewed for progression to persistent or permanent AF. Paroxysmal, persistent and permanent AF was defined according to the ACC/AHA guidelines.<sup>17</sup> Spontaneous conversion of AF to sinus rhythm or termination within 24 hours of onset was considered paroxysmal. If cardioversion was required or if AF persisted beyond 7 days, it was classified as persistent. AF refractory to cardioversion and long lasting AF was classified as permanent AF. Patients who presented to the ER within 7 days of onset of symptoms and were cardioverted were classified as persistent and were excluded from the study if this was the first episode. Patients presenting to the ER with a new episode of AF with remote history of cardioversion were also excluded. Patients whose history could not be confirmed were excluded.

Electronic medical records of patients with PAF

thus obtained were reviewed for clinical and demographic information. They were divided into two groups. Group 1 included patients who progressed to persistent or permanent AF. Group 2 included patients who continued to remain in PAF till April 2009. Differences in baseline demographic and clinical characteristics between the two groups were identified. BMI, LA size, left ventricular size, pulmonary artery (PA) pressure, ejection fraction and serum creatinine were analyzed as continuous variables while the remainder of the variables were analyzed as categorical variables. Diastolic dysfunction and valvular heart disease (VHD) were analyzed as binary variables and were considered as present when echocardiographic findings reported moderate to severe dysfunction (Grade 2 and grade 3 of diastolic dysfunction and moderate to severe mitral and aortic valve disease). Cardiomyopathy was defined as present if any patient had a documented diagnosis of ischemic, non-ischemic or hypertrophic obstructive cardiomyopathy in the medical record. Medication use was considered at baseline when patients had PAF and had not yet progressed. Mortality data was obtained from social security death index.

## Statistical Analysis

Categorical data is expressed as percentages and continuous data as means and standard deviation. Chi-square analysis and t-tests were performed for categorical and continuous data respectively. Univariate logistic regression analysis was performed to identify univariate predictors of progression to persistent and permanent AF. Multivariate logistic regression was then performed from univariate predictors. A p value of 0.15 from univariate analysis was considered significant to enter into the regression model. A sub analysis was then performed to identify the univariate and multivariate predictors of progression to persistent AF and permanent AF separately. P value of 0.05 was considered significant. SAS 9.1.3 version (SAS Institute Inc, Cary , NC ) was used for the analyses.

## Results

BA total of 437 patients were identified to have PAF. Among these patients 32.4% (n=142) progressed to persistent or permanent AF over a

mean duration of  $57.5 \pm 55.3$  months (group 1). The remaining 67.5% ( $n=295$ ) of patients continued to be in PAF (group-2) followed over a mean of  $90.7 \pm 60.5$  months. Mean age of the population was  $67.9 \pm 13.4$  years with 57% males and 92% Caucasian origin. Mean EF was  $52 \pm 16\%$ . Mean LA size was  $4.2 \pm 0.7$  cm. See table 1 for baseline characteristics in the two groups. Mean duration of follow-up in group 2 patients with PAF was 7.5 years (median 82 months, range 7- 425 months). Minimum, maximum and median follow-up duration in the group 1 was 1 month, 215 months and 38.2 months respectively.. Univariate analysis identified higher body mass index (BMI), diabetes, cardiomyopathy, valvular heart disease, larger LA size and higher PA pressure as predictors of progression (See table 2). Multivariate logistic regression analysis revealed larger left atrial size (OR 1.46, CI 1.05-2.04,  $P$  0.02), cardiomyopathy (OR 2, CI 1.2- 3.3,  $P$  0.009), and moderate to severe VHD (OR 3.3, CI 1.6-5,  $P$  0.0014) as significant predictors of progression to persistent/permanent AF. There was no difference in mortality in both groups 1 and 2 (10.4% vs. 10.5%,  $p$  0.99). Similarly there was no significant difference in the incidence of stroke between group 1 (0.25%) and group 2 (0.01%).

Among the 142 patients who progressed to persistent/permanent AF, 111 patients (78%) progressed to persistent AF and 44 patients (31%) progressed to permanent AF. Of the 44 permanent AF patients, 11 patients initially turned persistent who then converted to permanent AF while the rest of 33 patients directly progressed from PAF to permanent AF (Figure 1). On sub-analysis, univariate predictors for progression to persistent AF were higher BMI, larger LA size, VHD and cardiomyopathy. Predictors of progression from PAF to persistent AF on multivariate analysis were higher BMI (OR 1.05, CI 1.01-1.09,  $P$  0.01) and cardiomyopathy (OR 2.5, CI 1.25-5,  $P$  0.008).

Predictors for progression from paroxysmal to permanent AF alone were also studied which showed larger LA size, higher PA pressure, VHD and cardiomyopathy as univariate predictors and larger LA size (OR 2.4, CI 1.3-4.2,  $P$  0.002) and VHD (OR 3.1, CI 1.3-7.6,  $P$  0.008) as multivariate predictors. Mean LA size in patients with PAF was  $4.1 \pm 0.7$  cm while the mean LA size in patients who progressed to permanent AF was  $4.7 \pm 0.7$  cm.

The 11 patients who progressed from persistent to permanent AF were not included in this analysis and their number was too small to define this group of patients.

## Discussion

Our results indicate that larger LA size, moderate to severe VHD and cardiomyopathy predict progression of PAF to persistent or permanent AF. Higher BMI and cardiomyopathy predicted progression to persistent AF while larger LA size and VHD predicted progression to permanent AF.

While prior studies have looked at the progression of PAF to chronic AF<sup>8, 18</sup> our study evaluated the predictors of progression to persistent and permanent AF separately. Also, previous studies did not include many potentially predictive echocardiographic and treatment variables although they were observational studies.<sup>19, 20</sup> In our study we have included a comprehensive list of echocardiographic and treatment variables to study their effect on AF progression.

Thirty two percent of patients with PAF progressed to persistent/permanent AF in our study which is slightly higher than the 20% progression rate noted in an European survey.<sup>21</sup> Our study results are similar to a Canadian cohort study where age, presence of cardiomyopathy, larger LA size and valvular disease were identified as significant predictors.<sup>18</sup> Our study is further distinguished by the inclusion of all echocardiographic and treatment factors in the statistical model.

Although age is a known risk factor for AF, our study did not identify age as a predictor of progression to permanent AF. The average age of patients in our study was 68 years. Risk factors that predict progression can generally be classified in to modifiable risk factors and non- modifiable risk factors. While age is an unmodifiable risk factor, the other factors (LA size, cardiomyopathy and VHD) identified in our study could be modified to some extent by early intervention. Identification of modifiable risk factors is important to design interventions that prevent progression of AF by targeting these risk factors. Cardiomyopathy and valvular heart diseases cause increased left atrial pressure and wall stretch. Larger left atrium in turn perpetuates of AF.

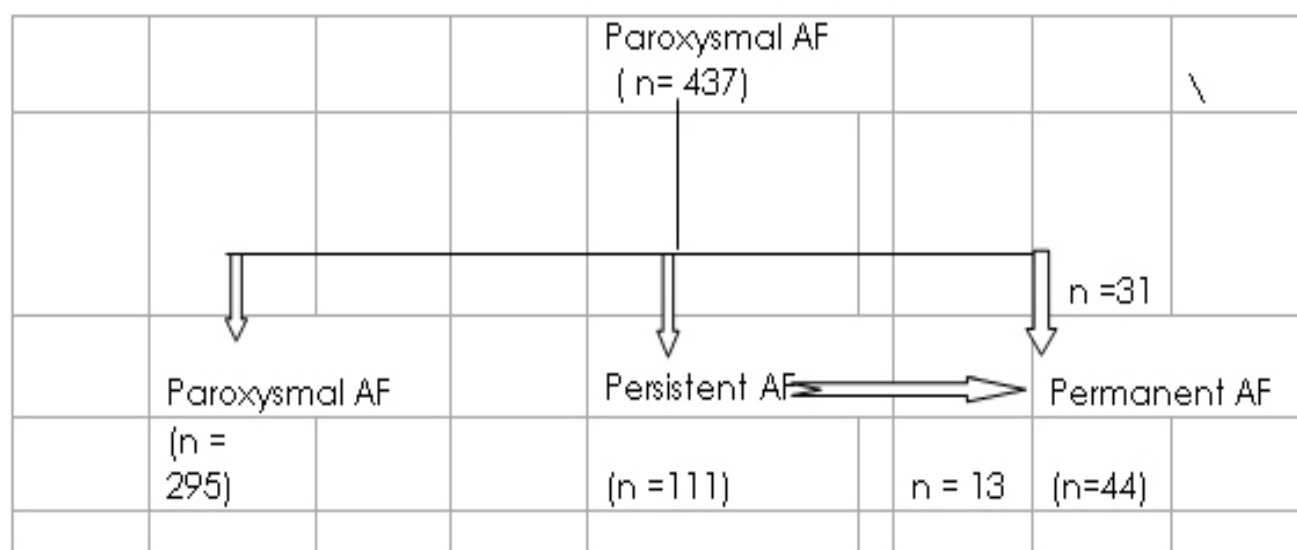
This is supported by recent studies which suggest that structural changes of the heart result in substrate changes that support reentrant tachycardias.<sup>22</sup> In fact, even in lone AF patients, one recent study demonstrated abnormalities in the atria. The study showed electrophysiologic and electroanatomic abnormalities like atrial dilatation, lower mean atrial voltage, prolonged conduction times, slower conduction velocities, impaired sinus node function and increased effective refractory period disputing the role of electrical remodeling as the cause of perpetuation of AF and argue that these changes termed as the “second factor” contribute to perpetuation of AF more than the electrical remodeling in itself.<sup>23</sup> Hence it is all the more important to prevent and treat the underlying structural changes in the heart like the larger LA size, cardiomyopathic changes and changes brought about by VHD. Interventions such as optimal treatment of cardiomyopathy, attempts at reduction of diastolic pressure to reduce LA size and early surgical treatment of valvular diseases may prevent the progression to persistent/permanent AF. In addition to these secondary prevention strategies, primary prevention strategies can also be employed before onset of AF.

On subanalysis, BMI and cardiomyopathy were found to be a predictor for progression to persistent AF in our study. BMI has also previously been shown to be a risk factor for progression in a recent study.<sup>24</sup> Several reasons were cited for this

including neurohormonal activation, obstructive sleep apnea, arterial thickness and increased inflammation related to obesity.<sup>25-27</sup> Thus attempts at reducing the BMI are also helpful in preventing progression of this disease and larger randomized therapeutic trials directed at this issue are needed. LA size and VHD have been identified as predictors of progression to permanent AF by multiple studies including ours.<sup>8,18</sup> These factors probably induce underlying substrate changes that promote progression of AF to a more permanent form without going through the persistent stage. It is important to understand that left atrial enlargement is a primary manifestation of uncontrolled HTN, diastolic dysfunction, VHD and cardiomyopathy. Attempts could be made to prevent left atrial enlargement by early and effective treatment of the above mentioned risk factors. Early ablation of PAF may also prevent LA enlargement and thus prevent the progression to permanent AF. A recent study by Pappone et al. showed the effectiveness of catheter ablation in preventing the progression of PAF.<sup>28</sup> Age related progressive left atrial enlargement may not be modifiable; however all the above mentioned factors become increasingly apparent in older patients. Early surgical treatment of mitral and aortic valvular diseases would also help prevention of AF progression.

We hoped to see a positive impact from the use of statins and ACE inhibitors, which have been shown to prevent occurrence of AF possibly by

**Figure 1:** Comparison of AF patients who progressed to persistent/permanent AF vs those who did not progress.



modifying the atrial substrate.<sup>29-31</sup> Hirayama et al have shown that ACE inhibitors are effective in preventing AF progression.<sup>32</sup> In our study that mostly consisted of a Caucasian American population, ACE inhibitors/ARBs failed to show this effect. Our study also failed to show any effect of statins or AAT agents on progression of the dis-

ease. Similarly nicotine use which has been shown to induce atrial fibrosis failed to show any affect on the progression of AF in our study.<sup>33</sup> This is possibly related to the relatively smaller number of patients studied. Further studies need to be done prospectively on large patient numbers to study the mechanics of progression of the disease. Specifically a

**Table 1** | Comparison of AF patients who progressed to persistent/permanent AF vs those who did not progress.

Clinical Characteristics	Group 2 N =295	Group 1 N = 142	P
Age (years)	67.5	68.2	0.6
Body mass index (BMI)	28.8±6.5	29.8±6.5	0.12
Gender (%)	57.5	58	0.9
Caucasian (%)	96.4	96.4	0.9
Beta-blocker (%)	74.5	74.6	0.9
Aspirin (%)	70	71.8	0.66
ACE+ARB (%)	54	55.6	0.7
Proton pump inhibitor (%)	29.4	33.8	0.36
Anti-arrhythmic therapy (AAT) (%)	55.5	52.1	0.4
Statin (%)	56.6	50.7	0.2
History of myocardial infarction (%)	19	17.7	0.7
Hypertension (%)	66.1	69.7	0.45
Diabetes mellitus (DM) (%)	1.00 (0.99–1.00)	23.2	0.06
Stroke (%)	12.5	17	0.2
Cardiomyopathy (%)	17.6	36.6	<0.0001
COPD (%)	9.1	7.1	0.4
Diastolic dysfunction (%)	11.1	8.5	0.4
Hyperlipidemia (%)	57	62	0.3
Obstructive sleep apnea (OSA) (%)	15.6	16.2	0.8
Valvular Heart Disease (VHD) (%)	9.5	22.5	0.0002
Smoking (%)	46.3	39.2	0.17
Alcohol (%)	35.5	30.4	03
Creatinine (mg/dl)	1.1±0.39	1.1±0.35	0.6
Left ventricular end diastolic diameter (cm)	4.8±0.7	4.8±0.7	0.8
Left Ventricular end systolic diameter (cm)	3.1±0.8	3.3±0.8	0.2
Ejection Fraction (%)	53.5±16.3	51.4±15.2	0.18
Left Atrial (LA) size (cm)	4.1±0.7	4.4±0.7	0.0003
Pulmonary Artery Pressure (mm Hg)	33.6±9	35.7±9.5	0.04

**Table 2** Predictors of AF progression from paroxysmal to persistent or permanent form by Uni- variate Analysis

Variables	Odds ratio	CI	P value
BMI	1.025	0.99-1.05	0.12
Cardiomyopathy	2.689	1.7-4.2	<0.0001
DM	1.5	0.9-2.6	0.06
LA	1.7	1.2-2.3	0.0004
VHD	2.7	1.5 – 4.8	0.0003
PA pressure	1.02	1-1.04	0.04

large prospective study evaluating the impact of statins, angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARBs), beta blockers (BB) and anti-arrhythmic agents (AAT) on progression of AF is very essential. Our study also highlights a group of people who converted to permanent AF from PAF without going through the persistent stage. Mechanisms that underlie this phenomenon should also be studied.

### Study Limitations

This is a retrospective study. Clinical information is based on electronic medical review and was thus dependent on documentation. However, the long duration of follow-up provided strength to the study.

### Conclusions

Moderate to severe valvular heart disease, larger left atrial size and cardiomyopathy predict progression of PAF to persistent/permanent AF. While higher BMI and cardiomyopathy predict progression to persistent AF, larger LA size and significant VHD predict progression to permanent AF directly. Prospective randomized studies that evaluate modifiable risk factors are needed and studies should be geared towards understanding the mechanism of LA enlargement.

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