# Thromboembolic Outcomes in Patients with Atrial Fibrillation on Two Year Follow Up

Praveen Satheesan[1], Veena Felix[2], Alummoottil George Koshy[3]

[1]Department of Cardiology, Government Medical College, Thiruvananthapuram, Kerala, India. [2]Department of Cardiology, Government Medical College, Thiruvananthapuram, Kerala, India. [3]Department of Cardiology, Government Medical College, Thiruvananthapuram, Kerala, India.

## ABSTRACT

### BACKGROUND

Atrial Fibrillation is a common arrhythmia especially in patients with valvular heart disease, hypertension, heart failure, and chronic obstructive lung disease. Aim of this study is to assess the clinical outcomes of thromboembolic events such as stroke, transient ischemic attack, myocardial infarction and peripheral embolism in patients with atrial fibrillation on a 2 year follow up in a tertiary care center in India.

### METHODS

Individuals diagnosed with atrial fibrillation in both outpatient and inpatient department were included. A total of 329 patients was included and followed up for 2 years and analysed for outcomes.

### RESULTS

Permanent AF was diagnosed in 42.6 % (n = 140), persistent in 23.1 % (n = 76) and paroxysmal in 34.7 % (n = 113). Valvular AF (moderate and severe mitral stenosis, prosthetic mechanical valve) was present in 26.7 % (n = 88) and nonvalvular AF in 73.3 % (n = 241). 74.8 % (n = 246) of AF patients were on oral anticoagulants and 4 were on NOAC. During 24 months of follow up, 26 patients (7.9 %) developed thromboembolic events. All were ischemic stroke and 4 were fatal stroke. 4 of these patients defaulted anticoagulants. Time in therapeutic range >60 % (good control) was present in only 3 out of the 26 patients.

### CONCLUSIONS

Though majority of the patients were on oral anticoagulants, they were not under good control (subtherapeutic INR). Frequent monitoring with adequate anticoagulation and adherence to therapy can improve the outcomes in AF patients.

### KEYWORDS

Thromboembolism, Stroke, Atrial Fibrillation, Anticoagulants

## BACKGROUND

Atrial fibrillation is a common arrhythmia encountered in clinical practice. It results from unorganized atrial activity resulting in irregularly irregular ventricular contractions and heart rhythm. Previous studies suggest that rheumatic valvular heart disease is more common cause in India than the western population. Valvular heart disease is independently associated with incident A.F.[1] Other causes include conditions with elevated atrial pressures such as hypertension, heart failure, pulmonary hypertension, chronic obstructive pulmonary disease, obstructive sleep apnoea, thyroid disorders. The prevalence of atrial fibrillation increases as aging population increases.[2] It affects over 4 percent of the population above the age of 60 years.[3] Lone atrial fibrillation (AF) (i.e. without underlying cause), is observed in up to 10 % of patients with AF.[4]

Paroxysmal AF (PAF), also termed intermittent AF, is defined as an episode of AF that terminates spontaneously or with intervention in less than seven days.[5] Persistent AF lasts more than a week. Persistent AF sustains irrespective of whether the arrhythmia is terminated by any therapy or cardioversion has not been attempted. Term Permanent AF is used when there has been a joint decision by the patient and clinician to cease further attempts to restore and/or maintain sinus rhythm.

The clinical knowledge and physician preference as well as the adherence to therapy have a great impact in the management and outcomes in patients with atrial fibrillation. Thromboembolic events, heart failure and bleeding risks of anticoagulants are the main concerns in treatment of atrial fibrillation.

The AHA/ACC/HRS 2014 guidelines for Atrial Fibrillation use the $CHA_2DS_2$-VASc score. It is used in patients with nonvalvular AF. Cardiac failure, Hypertension, Diabetes mellitus has 1 point each and age >75 years and previous Stroke (CVA and transient ischemic attack) has 2 points each, vascular events, second A for age 65-74 years and Sc for female sex has 1 point each. If score is <2 then aspirin therapy is given and if the score is ≥2 anticoagulants are given for the prevention of thromboembolic events. Oral Anticoagulants significantly reduced stroke in patients with AF.[6]

### Objective
To estimate the incidence of thromboembolic events such as stroke, transient ischemic attack, acute coronary syndrome and peripheral embolism in people with AF during 2 years follow up.

## METHODS

This is a cross sectional study conducted from April 2016 to May 2019, at Medical College Hospital, Thiruvananthapuram, after approval from Institutional Ethical Committee.

### Inclusion Criteria
- Subjects with diagnosis of atrial Fibrillation either on follow up or newly diagnosed (incident cases) attending the cardiology outpatient or inpatient department, Trivandrum Medical College, Kerala.
- Age 18 years to 80 years.

### Exclusion Criteria
Atrial fibrillation in critically ill patients with life expectancy less than 1 week.

### Sample Size
Formula for calculating sample size.

$$n = \frac{Z_1^2 - \frac{a\,P(1-p)}{2}}{\delta^2}$$

With reference to the similar study[7] p = 8.8 %, "proportion of stroke among AF patients"
   p   : Expected proportion (8.8 %)
   δ   : Absolute precision (3 %)
   1-α/2 = Desired Confidence level = (95 %)

So, sample size fixed is 314, rounded of to 320.

Informed written consent was obtained from patients. Baseline characteristics like age, gender, demographics, heart rate, blood pressure, type of AF, ECG parameters and date of diagnosis, were recorded in a predesigned case record form. Patients were followed up by interview or telephonic contact at 1 month, 3 months, 6 months, 12 months and 24 months for treatment adherence, investigations (INR values), and development of complications. Time in therapeutic range of INR calculated by traditional method. Appropriate statistical tests (Mean, S.D., Median t-test for quantitative/continuous variables and proportions, Chi-square test and odds ratio for qualitative variables) were conducted with the help of Excel 2010 and SPSS 16 statistical software.

## RESULTS

In this study, 329 patients with atrial fibrillation were followed up for 24 months. There were 199 female patients (60.5 %) and 130 male patients (39.5 %). Age distribution is as given in the table below. Average age is 60.56 years. 241 patients had nonvalvular AF (73.3 %) and 88 were valvular AF (26.7 %). Types of AF were as follows- Paroxysmal AF in 113 (34.3 %), permanent AF in 140 (42.6 %) and persistent AF in 76(23.1 %). 164 patients had CHADS2VASc score more than or equal to 2. 246 patients (74.8 %) were on anticoagulation of which 4 were on Novel Oral Anticoagulants and 242 patients on oral vitamin K antagonists. 112 patients were taking aspirin.

Over 24 months follow up of these patients, 26 patients (7.9 %) developed stroke, all of which were thromboembolic and 4 of them were fatal stroke. One among them had haemorrhagic transformation.

Proportion of INR between 2-3 among these 26 patients during 2 year follow up was 37.4 %. The mean time in therapeutic range (TTR) with INR values between 2 and 3 was calculated by Traditional method. 4 patients had only 1 INR value. Time in therapeutic range ≥60 % (good control) was present in only 3 of these patients. Time in therapeutic range of rest of the 23 patients were <60 %.

3 of them were valvular AF and 23 patients were nonvalvular AF. All were started on oral anticoagulants. 4 patients discontinued anticoagulants before the event of stroke. Of these 26 patients with stroke, 4 patients expired. 5 were recurrent stroke i.e., in those with previous history of stroke. There was no occurrence of new peripheral embolism, limb ischemia or acute coronary events among these patients.

| Age in Years | Frequency | Percentage |
|---|---|---|
| <50 | 51 | 15.5 % |
| 50 - 59 | 81 | 24.6 % |
| 60 - 69 | 118 | 35.9 % |
| 70 - 79 | 75 | 22.8 % |
| ≥ 80 | 4 | 1.2 % |
| Total | 329 | 100 % |
| **Table 1. Age Distribution of AF Patients** | | |



Figure 1. Stroke in AF Patients with Age Distribution
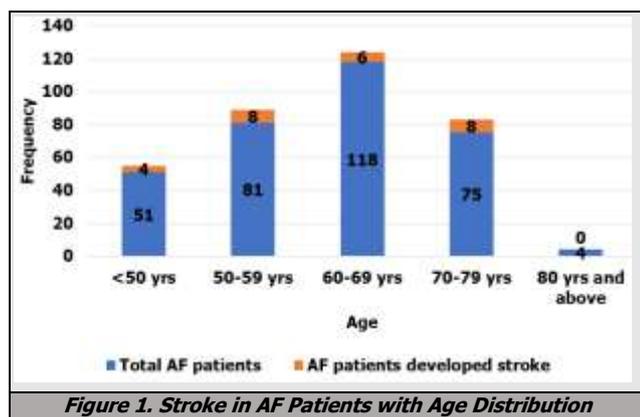
## DISCUSSION

Atrial Fibrillation is an important risk factor for thromboembolism. Fibrillating atria forms a source of atrial and appendage thrombi. Other factors in AF patients which contribute to thrombus formation are valvular heart disease such as mitral stenosis, mechanical prosthetic heart valve, associated heart failure, left atrial dilatation etc. The atrial and appendage thrombi can dislodge and shed showers of emboli to the systemic circulation such as the cerebral, coronary, renal and peripheral arteries. Healey et al. showed that rates of stroke occurrence within a year of presenting with AF at a hospital emergency department according to the countries were as follows: North America, Western Europe, or Australia (2 %), South America (3 %), Eastern Europe (4 %), Southeast Asia (7 %), China (7 %), Africa (8 %), and India (0.8 %).[8] Risk of ischemic stroke after atrial

fibrillation diagnosis during follow-up was 9.6 % during a mean follow up period of 3.2 years.[9] At 2 year follow up in our study, stroke occurred in 7.9 % while 1.03 % patients had stroke in the IHRS-AF Registry during 1 year follow up.[10]

The Framingham study and others have demonstrated a fivefold increase in overall stroke risk associated with AF.[11] The proportion of stroke associated with AF increases progressively with age, ranging from 6.7 % in individuals aged 50–59 years to 36.2 % in those aged 80–89 years.[12,13] In our study stroke occurred with increased frequency in age group 50 and above (22 patients).

The risk of thromboembolism is same in patients with paroxysmal, persistent and permanent atrial fibrillation. In this study stroke occurred in 10 patients with paroxysmal AF, 5 patients with persistent AF and 11 patients with permanent AF. Data from the Stroke Prevention in Atrial Fibrillation (SPAF) study[14] showed that patients who had paroxysmal atrial fibrillation and at least one risk factor for thromboembolism had stroke rates comparable to those with persistent and permanent atrial fibrillation.

Among patients who developed stroke, 3 patients had valvular AF and 23 patients had nonvalvular AF, out of which 16 patients had CHADS2VASc score ≥2. All patients with valvular AF (i.e. Moderate to severe Mitral stenosis and mechanical prosthetic valve) should be anticoagulated. CHADS2VASc scoring system helps in risk stratification of nonvalvular AF patients for anticoagulation. Oral Anticoagulants significantly reduced stroke in patients with AF.[7] In our study though anticoagulants were given to all 26 patients who developed stroke 4 were drug defaulters and majority were in subtherapeutic range of INR based on Time in therapeutic range. Use of oral anticoagulants and the underdoing in these AF patients at risk for stroke are limited by infrequent access to INR testing, follow-up, other factors like increased risk of bleeding and noncompliance to medications. The advent of novel oral anticoagulants may help to overcome some of these barriers; however, their current high costs may make these novel drugs affordable for only a selected group of individuals. AF related strokes are more likely to develop significant disability. Moreover, AF-related strokes are 2.5-fold more likely to be fatal.[15] 4 of our patients developed fatal stroke. Oral anticoagulation has been shown to reduce the risk of stroke by 64 % and the risk of death by 26 % in patients with AF. None of our patients on follow up developed thromboembolic events other than stroke. The incidence of SEEs (0.24/100 person-years) was lower than cerebral embolism (1.92/100 person-years) in previous studies.[16]

## CONCLUSIONS

Though majority of patients were on anticoagulation medications, the therapeutic range of INR and time in therapeutic range were subclinical. Subtherapeutic anticoagulation is a major issue in the treatment of AF patients. This could have attributed to the high incidence of

stroke in this study population. In AF patients, frequent monitoring with adequate anticoagulation and adherence to therapy can prevent adverse outcomes.

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