

Observational Study

# Prevention of Atrial Fibrillation using Vaughan Williams Class IC Drugs for Multiple Premature Atrial Contractions: A Clinical Observational Study

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## Abstract

**Background:** Atrial fibrillation (A-Fib) poses a significant clinical challenge, particularly in the elderly and those with hypertension. If A-Fib represents one stage in the spectrum of electrical degeneration caused by aging-induced remodeling of the left atrial wall, catheter ablation is not an essential treatment. The efficacy of Vaughan Williams Class IC drug in preventing the progression of multiple premature atrial contractions (mPAC) toward paroxysmal atrial fibrillation (PAF) and A-Fib in the earlier stage of histological change was investigated.

**Method and results:** Group A (4 patients with mPAC) and Group B (9 patients with PAF) were treated with Class IC drugs. Treatment outcomes were compared between these two Groups and Group C (8 patients with chronic A-Fib).

Follow-up assessments were performed to evaluate the maintenance of sinus rhythm.

All mPAC patients maintained sinus rhythm during the follow-up period. In the PAF group, 8 out of 9 patients maintained their sinus rhythm.

**Conclusion:** Early treatment with Class IC drugs shows promise in preventing the progression of A-Fib and maintaining sinus rhythm in patients with mPAC and PAF. These findings highlight the potential role of pharmacological therapy in delaying the onset of A-Fib, thereby improving clinical outcomes and reducing the need for invasive procedures such as ablation.

## Introduction

Atrial fibrillation (A-Fib) is commonly associated with mitral stenosis and hyperthyroidism, but it predominantly manifests as an aging-related disorder, exhibiting a pronounced prevalence among the elderly and hypertensive individuals. Often insidious in onset, A-Fib frequently remains asymptomatic until its detection following cerebral infarction.

In 1998, Haïssaguerre, et al. elucidated the pulmonary vein as the primary origin of A-Fib [1]. Their pioneering work revealed that ectopic impulses emanating from the pulmonary veins trigger A-Fib, and subsequent studies demonstrated the efficacy of radiofrequency catheter ablation in targeting these ectopic foci. Nevertheless, the precise pathophysiological mechanisms governing the development and perpetuation of A-Fib remain

incompletely understood. Given the challenges in returning to complete sinus rhythm once A-Fib is established, the author proposed aggressive treatment of multiple premature atrial contractions (mPAC) as a strategy to delay atrial muscle aging and remodeling, essential for A-Fib management. This study aimed to investigate whether mPAC treatment with Class IC (Vaughan Williams Classification) [2] drugs can prevent progression to A-Fib.

## Patients and methods

### Study design and patients

This clinical study enrolled four patients (Group A) exhibiting mPAC without structural abnormalities (Table 1), along with nine newly diagnosed patients with paroxysmal atrial fibrillation (PAF) (Group B) (Table 2), and eight additional patients diagnosed with chronic A-Fib (Group C) (Table 3). Patients in Groups A and B were

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**Keywords:** Atrial fibrillation; Premature atrial contraction; Prevention; Class IC



**Table 1:** Multiple premature atrial contractions (mPACs) in Group A.

Case No.	Age at diagnosis of mPAC (years)	Sex	Sinus rhythm maintenance period <sup>†</sup>	Comorbidities	Outcome
1	44	F	7 years 8 months		Sinus rhythm
2	69	M	5 years 3 months	Hypertension	Sinus rhythm
3	65	M	4 years 9 months		Sinus rhythm
4	61	M	2 years 3 months	Hypertension	Sinus rhythm

<sup>†</sup>:As of the end of September 2024.

**Table 2:** Paroxysmal atrial fibrillation (PAF) in Group B Paroxysmal atrial fibrillation (PAF) in Group B.

Case No.	Age at diagnosis of PAF (years)	Sex	Sinus rhythm maintenance period <sup>†</sup>	Comorbidities	Outcomes
1	41	M	11 years 3 months	Hypertension	Sinus rhythm PVC
2	46	F	10 years 10 months		Sinus rhythm
3	48	M	7 years 10 months	Hypertension	Sinus rhythm
4	81	F	3 years 8 months	C	Sinus rhythm
5	64	M	3 years 5 months	63 y-o. PAC Hypertension	Sinus rhythm
6	56	M	1 year 8 months	Hypertension	Sinus rhythm
7	78	F	1 year 1 month	Hypertension	Returned to A-Fib in 6 months. Changed to Ablation
8	44	M	1 year 3 months		Sinus rhythm
9	60	M	1 year 1 month	Hypertension	Sinus rhythm

<sup>†</sup>: As of the end of September 2024. PVC: Premature Ventricular Contraction; PAC: Premature Atrial Contraction.

**Table 3:** Permanent atrial fibrillation in Group C.

Case No.	Age at diagnosis of PAF (years)	Sex	History of treatment	Comorbidities	Outcomes
1	73	M	Post ablation	Hypertension	Several types arrhythmia
2	62	M	Post multiple ablations	Hypertension	A-Fib/A-Fl
3	53	M	Post ablation	Hypertension	No effect of ablation
4	79	M	Class IC is not effective	Hypertension	Permanent A-Fib
5	38	M	Ignored the advice of the doctor 10 years ago	Hypertension	Permanent A-Fib
6	75	F	Accepts only aspirin	Hypertension	Permanent A-Fib
7	67	M	Accepts only DOAC		Permanent A-Fib
8	63	M	Refused ablation Accept warfarin	Hypertension	Permanent A-Fib

A-Fl: Atrial Flutter; DOAC: Direct Oral Anticoagulant

diagnosed with mPAC or PAF based on electrocardiogram findings, often detected incidentally during outpatient visits for hypertension or through symptoms such as palpitations. Class IC drugs were administered solely to patients over 40 years of age without ischemic heart disease who consented to treatment. Patients with ischemic heart disease were not enrolled based on the results of the CAST study [3]. Group C comprised patients with chronic A-Fib undergoing anticoagulant therapy with rate-controlled treatment or those continuing medication following unsuccessful ablation. The author compared the ability of patients in Groups A and B to maintain sinus rhythm or progress to permanent A-Fib with that of patients in Group C comprehensively evaluating treatment outcomes. Additionally, the presence or absence of side effects associated with Class IC drugs was examined.

## Therapy

The Class IC drugs utilized in this study included pilsicainide and flecainide.

The author elected the drugs because Class IC drugs are the slowest to bind and dissociate to Na channels, minimize the speed of depolarization, do not extend the duration of action potentials, and have a strong blocking effect [4]. It is effective in suppressing the recurrence of mPAC as well as PAF and has fewer side effects than Class

III drugs. In Japan, the initial prescription of pilsicainide or flecainide for tachyarrhythmia is restricted to cases in which other drugs are ineffective, so they were prescribed after a short course of beta-blockers.

## Results

### Group A

Results of patients with mPAC (Table 1). Follow-up was conducted on an outpatient basis, confirming arrhythmia through auscultation or electrocardiogram. Implantable electrocardiogram recorders were not utilized. Over the course of observation (ranging from 2 years to 7 years and 3 months), all patients with mPAC maintained sinus rhythm, with no occurrences of A-Fib.

### Group B

Regarding outcomes of Class IC drug treatment for PAF, among Group B patients, one of the nine patients underwent ablation after 6 months due to the ineffectiveness of Class IC drug treatment. Following ablation, supraventricular arrhythmias recurred initially but have recently subsided, maintaining sinus rhythm. The remaining eight patients (observed from 8 months to 10 years and 10 months) sustained sinus rhythm, with two maintaining it for over 10 years.



Regarding side effects of Class IC drugs, one patient who was administered the drug for 10 years, switched to flecainide due to gastrointestinal issues from pilsicainide. No other adverse effects were noted. Electrocardiogram analysis revealed instances where patients initially without hypertension displayed a decrease in SV1 + RV5. The widening of the QRS wave is not evident. This phenomenon may be attributed to antihypertensive drug treatment. No cases of atrial flutter occurred. NT-ProBNP values remained within the normal range.

### Group C

Among Group C cases, three patients underwent ablation at different medical facilities and were subsequently followed up at our clinic. Case 1 underwent a single ablation and subsequently experienced repeated episodes of atrial fibrillation and various arrhythmias. Case 2 underwent ablations several times, but continued to develop atrial fibrillation, atrial flutter, and PVC. Case 3 had permanent A-fib and it was expected that recovery of sinus rhythm would be impossible, but the patient dared to request ablation, which was unsuccessful as expected. Case 8 was recommended ablation but refused. All patients are alive, but in Case 8, cardiac enlargement and pleural effusion were observed, and diuretic treatment was performed.

## Discussion

In real-world clinical practice, A-Fib is often identified through electrocardiogram readings coupled with palpitations or during routine medical examinations where abnormal heart sounds are detected. Its most perilous manifestation occurs when it leads to thromboembolism, such as cerebral infarction, and is diagnosed only after a secondary disease emerges.

### Classification of A-Fib

A-Fib is categorized as paroxysmal, persistent, long-standing, or permanent. However, the reality is that these latent irregular contractions associated with A-F-b are often serendipitously discovered or when symptomatic.

### Treatment

Regarding treatment, previous Japanese guidelines suggest that primary A-Fib without underlying heart disease may not necessarily require interventions to prevent recurrence due to the limited recurrence rate [5]. Nevertheless, during the acute phase, restoring sinus rhythm or regulating heart rate is imperative [6].

The Japan Cardiovascular Society/Japan Arrhythmia Electrocardiology Joint Guidelines 2022 Revised -Arrhythmia Drug Treatment Guidelines delineate the procedure for restoring sinus rhythm (defibrillation) and subsequent measures for preventing recurrence (sinus rhythm maintenance) in a flowchart [7]. Treatment approaches for A-Fib encompass both rhythm control and rate control strategies.

Two main approaches exist for rhythm control

treatment: drug therapy and non-drug treatment (such as ablation), with the latter gaining increasing popularity in recent times.

### Rate control treatment

Rate control treatment involves maintaining the heart rate within a moderate range. Without necessarily restoring sinus rhythm. Anticoagulant therapy typically constitutes the cornerstone of this approach.

In drug treatment, previous studies have predominantly focused on diverse patient populations including those with PAF, chronic A-Fib, and organic heart disease. However, the outcomes reported in these studies typically span a treatment observation period ranging from a few months to a maximum of five years. Although some reports have extended the follow-up duration to 14 years [8], these studies often involved mixed cohorts, making it challenging to statistically evaluate outcomes, particularly when considering PAF cases without concurrent organic heart disease, precisely the focus of this study.

### Ablation

Various ablation methods are utilized for treating PAF, including radiofrequency, hot balloons, frozen balloons, and Irreversible Electroporation (IRE). These techniques aim to disrupt the aberrant conduction pathways within the atrial muscle and target sites of ectopic beam firing. In the United States, a study reported a 74.6% success rate for restoring sinus rhythm after one year using the frozen balloon catheterization method, a relatively novel approach [9]. Similarly, after three years, the success rate for sinus rhythm restoration with frozen balloon catheterization in PAF patients was reported at 43.5% when assessed based on recurrence rates, which notably exceeded the 22.8% observed in the pharmacotherapy group, as documented by a Canadian study [10]. However a long-term follow-up study conducted in Italy over a span of 10 years revealed that 52% of patients experienced freedom from arrhythmias, while 10% developed permanent A-Fib [11]. The ultimate success of ablation lies in achieving sustained restoration of sinus rhythm, thereby obviating the need for ongoing antiarrhythmic medications and anticoagulants a rewarding outcome considering the invasiveness of the procedure.

As described above, the outcomes of non-drug intervention, such as ablation for PAF are often based on relatively short-term observation periods. However, despite these limitations, the success rate of restoring sinus rhythm typically ranges from 70% to 80%. This limitation may arise due to the logistical constraints associated with multicenter randomized controlled trials, which generally conclude within approximately five years. Consequently, the literature lacks extensive data exceeding the 10-year mark.

### Histological study

Studies have indicated that structural changes, including



thickening between cardiomyocytes due to fibrosis of the atrial muscle and enhanced non-uniform anisotropy conduction at gap junctions, tend to occur with advancing age [12-14]. Regarding left atrial fibrosis in patients with atrial fibrillation, there have been histological studies using left atrial muscle samples taken during the Maze procedure [15], as well as studies that non-invasively examined the extent of fibrosis using delayed enhancement MRI [16]. This suggests the potential development of asymptomatic structural alterations that spread diffusely across the atrial muscle, possibly leading to micro-reentry phenomena.

The atrial muscle is susceptible to micro-reentry due to diffuse tissue degeneration, potentially leading to the onset of A-Fib. Ectopic impulses originating from pulmonary veins or other sites are believed to contribute to the development of A-Fib. Despite interventions such as pulmonary vein isolation or direct ablation targeting these ectopic foci, recurrence is common due to the overall vulnerability to ectopic impulses. A-Fib itself may perpetuate its occurrence, as ablation only provides temporary relief or delay in its progression [17].

DECAAF study showed that among patients with A-Fib undergoing catheter ablation, atrial tissue fibrosis estimated by delayed enhancement MRI was associated with the likelihood of recurrent arrhythmia [16].

Given the frequent recurrence even after ablation, it is reasonable to consider A-Fib as a disease that has already advanced significantly and may not be completely curable. Furthermore, if PAF is perceived as an early-onset condition, it implies that the disease has already advanced considerably. In essence, it is crucial to acknowledge that A-Fib represents a disease that has progressed beyond its initial stages and may not respond effectively to conventional treatments.

While Alzheimer's disease primarily affects another organ, the onset of neuronal degeneration leading to its symptomatic manifestation typically initiates 10 years before clinical symptoms appear [18]. Similarly, it is plausible to infer that tissue alterations in the atrial myocardium progress gradually over time.

As highlighted earlier, PAF is a recent onset but rather considered a phenotypic expression of the disease, indicative of its gradual progression. Therefore, the question arises: when should interventions for A-Fib be initiated or emphasized?

### When treatment should be started?

Indications of atrial abnormalities serve as objective markers, including atrial extrasystoles observed on electrocardiograms and the enlargement of atrial diameter detected via echocardiograms. While atrial contraction is represented by the P wave on the surface electrocardiogram, the limited width and height of this wave hinder detailed analysis of atrial degeneration.

Premature atrial contractions (PACs) are also detected in healthy young individuals: however, their increased frequency among middle-aged and elderly populations warrants consideration as an abnormal phenomenon. It is common for frequent atrial extrasystoles observed in elderly and hypertensive patients to progress to A-Fib after a few years.

mPAC can often be detected in older adults with hypertension, potentially preceding the onset of A-Fib by several years [19-21]. This implies that mPAC serves as a precursor to A-Fib. Additionally, studies have indicated that Atrial-High-Rate Episodes (AHRE) are also linked to A-Fib, albeit differing from mPAC [22]. The development of a non-invasive method to detect subtle electrical changes in the atrium could facilitate the early identification of A-Fib.

Classifying A-Fib into categories such as paroxysmal, persistent, and long-lasting may make it seem as though A-Fib is a separate disease waiting to be classified. However, considering it as a latent and continuous condition, it's rational to regard mPAC and AHRE as part of a continuous spectrum of phenotypic expression. In 2023, U.S. academic societies revised their guidelines on A-Fib, finally acknowledging that PAC and other related phenomena serve as precursors to A-Fib [23]. However it does not clearly state when to start treatment.

1. Regarding new treatments, the author hypothesizes that A-Fib represents an amalgamation of electrical conduction impairment stemming from progressive aging-related atrial myopathy. To address this, the following preventive and therapeutic measures are suggested: Elderly patients with hypertension and frequent supraventricular extrasystole, but without ischemic disease, should be identified as A-Fib reserve patients and treated with drugs such as Class IC drugs.
2. Patients newly diagnosed with PAF should undergo an assessment to confirm the absence of ischemic disease and then promptly commence medication to maintain sinus rhythm.
3. In cases of PAF ineffective to Class IC drug treatment, ablation is recommended to attenuate the progression of atrial muscle remodeling. Subsequently, efforts are made to restore sinus rhythm as much as possible, followed by continued administration of Class IC medication to prevent recurrence.
4. Patients who achieve suppression of mPAC with Class IC drugs may experience a gradual reduction in their medication dosage over time. For instance, the frequency of pilsicainide intake can be decreased from three times daily to twice daily (morning and evening) or even once daily. Some patients may adopt a pill-in-pocket approach. This phenomenon can be attributed to reverse remodeling.



Maintenance of sinus rhythm in patients with mPAC is associated with a lower likelihood of requiring anticoagulants compared to patients with PAF. This offers the advantage of mitigating the risk of bleeding strokes.

There seems to be an overemphasis on non-drug treatments for A-Fib. This is because many cases of A-Fib encountered in clinical practice are already in the permanent stage, leading to poor outcomes with drug therapy. Indeed, attempts to restore sinus rhythm by prescribing Class IC drugs for persistent A-Fib often yield unsatisfactory results. Although Class III drugs are an alternative, they come with adverse effects on various organs, such as the lungs, liver, and thyroid, with complications like interstitial pneumonia being particularly severe. Consequently, cardiologists are increasingly opting for ablation over drug therapy.

Currently, treatment is initiated for both PAF and persistent A-Fib, but the author contends that these conditions have already progressed to a stage where reverse remodeling is unlikely. Ablation, though considered a treatment option, is far from minimally invasive, and there have been reported cases of death due to complications. In Japan, 20 fatal cases related to catheter ablation were reviewed in 2021 [24]. Pulsed field ablation [25], which is considered less invasive, is expected to cause less damage to surrounding organs, but the fundamental nature of ablation remains unchanged, and incidents of accidental complications, leading to deaths have been reported [26,27]. Should A-Fib be successfully treated with medication, ablation may not be a preferred treatment option.

Comparably, another medical intervention akin to ablation brings to mind vagus nerve resection for gastroduodenal ulcers, a procedure briefly prevalent in the 1970s [28]. This treatment addressed excessive gastric acid secretion, believed to be the primary cause of ulcers, in addition to *Helicobacter pylori* infection. Subsequently, H<sub>2</sub>-blockers and Proton Pump Inhibitors (PPIs) were developed and widely distributed as pharmaceuticals for controlling gastric acid secretion, rendering gastroduodenal ulcer surgery obsolete.

## Conclusion

In the future, as the fundamental cause of A-Fib becomes clearer and a minimally invasive drug treatment is developed, the need for ablation may diminish. Until then, the administration of Class IC drugs during the mPAC stage to curb atrial muscle remodeling progression could serve as a potential alternative to invasive ablation procedures.

Patients with mPAC and those with PAF may experience asymptomatic or transient sinus rhythm irregularities, leading to medication non-compliance, forgetfulness, or reduced adherence. It is crucial for patients to recognize the potential risks associated with their condition.

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## Ethical declarations

This study used a prescription drug that is often used in clinical practice, it was not considered to be a major risk.

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