



## **Catheter Ablation vs. Medical Therapy as First-line for Treatment of Symptomatic Paroxysmal Atrial Fibrillation: A Systematic Review**

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### **Authors' contributions**

*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

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### **ABSTRACT**

**Introduction:** The outcomes of Catheter Ablation (CA) and antiarrhythmic drugs (AAD) as the first-line treatment of paroxysmal Atrial Fibrillation (AF) are unclear. The current systematic review reports the evidence on efficacy outcomes of Radiofrequency Ablation (RFA) versus antiarrhythmic drugs (AAD) among these patients.

**Methods:** Three databases, including PubMed, Cochrane, and Google Scholar, were searched by three independent reviewers to identify relevant randomized control trials (RCTs).

**Results:** A total of 1,145 patients across five studies were assessed in this systematic review. Among these patients, 577 were randomized to receive ablation, and 568 were randomized to receive AAD. The recurrence rate was significantly higher among patients who received AAD at 1-year and 2-year follow-ups. The health-related quality of life (HR-QoL) was significantly better in the patients who received ablation therapy. The incidence of serious adverse events was 14 (6.4%) in the ablation group and 9 (4.3%) in the AAD group.

**Conclusion:** CA seems promising for managing AF in terms of any AF recurrence, hospitalization, and quality of life. There was no increase in side effects compared to AAD.

*Keywords: Radiofrequency ablation; antiarrhythmic drugs; atrial fibrillation; recurrence; hospitalization; adverse events.*

## 1. INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia expected to affect 6-12 million individuals in the United States by 2050 [1,2]. It is a progressive disease associated with an increased risk of heart failure and all-cause mortality [3]. AF has been linked with metabolic conditions such as overweight/obesity, metabolic syndrome, diabetes mellitus, and concurrent disorders such as sleep apnea [4,5]. Lifestyle factors have been associated with AF, including alcohol consumption and physical exercise [4,6]. AF is a risk factor for ischemic stroke and has strong epidemiological associations with heart valve disease and hypertension [7]. It is more common in the elderly population ranging from 10% to 17% in those aged >80 years compared to <1% in those aged <40 years [8]. The most frequent precipitants of AF are cardiac surgery (22%), pneumonia (20%), and non-cardiothoracic surgery (15%) [4,9]. Once diagnosed among patients, it has a high cumulative incidence rate of recurrence of 41% among individuals with a precipitant and 52% without a precipitant [4].

Current management guidelines for AF are unclear as the risk of recurrence and related morbidity remains unclear [10,11]. Antiarrhythmic drugs (AAD) are endorsed for AF before catheter ablation (CA) is considered [12]. However, the efficacy of AAD is not adequate and is associated with adverse events [13]. Certain studies demonstrate that CA is safer and non-inferior to AAD in reducing recurrence and maintaining sinus rhythm [14]. It has also been associated with improved quality of life and left ventricular ejection fraction (LVEF). In routine clinical practice, only patients refractory to AADs undergo CA. However, empirical literature adds to the support of CA as first-line in treatment-naïve individuals since shorter diagnosis-to-

ablation times improve outcomes such as rhythm control [15,16]. Whether CA improves clinical outcomes as the first-line treatment for AF patients requires further exploration. The following systematic review collates the latest evidence on efficacy outcomes of ablation vs. AAD among these patients.

## 2. METHODS

### 2.1 Search Strategy and Selection

We searched databases including PubMed, Scopus, and Embase from inception till July 10, 2022. A combination of MESH terms was run through Boolean operators, including "atrial fibrillation," "antiarrhythmic drug," "radiofrequency ablation," "cryoablation," and "first-line." Two investigators screened the studies for inclusion in the study. An umbrella review was also conducted to identify the studies from reference lists of all potential studies. First, the two investigators conducted a screening of the title and abstract. If there were discrepancies between the two investigators, a third investigator solved these with consensus. Second, the full texts were reviewed for eligibility against the selection criteria. There was no restriction on the search, such as time and language. Duplicates were removed using the software Endnote X9.

### 2.2 Selection Criteria and Endpoint

**Inclusion Criteria:** Randomized controlled trials (RCTs) and observational cohort studies (OCS) were considered. Only studies that reported patients older than 18, had symptomatic AF with at least one episode detected on electrocardiography (ECG) and were treatment-naïve were considered. We considered studies conducted in the last ten years, from 2012 to

2022; studies were considered if they had sufficient data with more than ten patients.

**Exclusion Criteria:** Studies included patients aged <18 years receiving antiarrhythmic drugs at therapeutic doses were excluded. Patients who were included with a left ventricular ejection fraction (LVEF) <40%, moderate-to-severe hypertrophy, and prior ablation for AF were also excluded.

The primary endpoint was the recurrence of any atrial fibrillation which is defined as symptomatic or asymptomatic atrial fibrillation that occurred within 90 days. This period was considered the blanking period, which was the time interval from index ablation or drug initiation based on the consensus statement by the Heart Rhythm Society. The secondary endpoint was the health-related quality of life (HR-QoL), incidence of asymptomatic atrial tachyarrhythmia recurrence, and incidence of serious adverse events following CA or AAD.

### 2.3 Data Management and Analysis

Two investigators extracted data from the finalized studies using Excel's custom datasheet. The variables were pre-tabulated based on the consensus from three investigators. They included study design, follow-up duration, outcomes, total sample size, CA sample size, AAD sample size, age, male, CVD risk factors, type of AF, the procedure of CA, method of monitoring, and outcome measures. All three reviewers utilized the Cochrane Risk of Bias (ROB) tool, and a qualitative analysis was conducted.

## 3. RESULTS

A step-by-step approach to the search strategy was reported as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. The overall search process is summarized in Fig. 1. In the first phase, 997 records were identified through different databases. After removing duplicates, 854 papers were screened for potential eligibility by titles and abstracts. In the second phase, 829 records were excluded, and 25 records were screened for full-text eligibility. In the final stage,

five studies were included in the qualitative analysis.

The key characteristics of the studies included in the review are summarized in Table 1. Five studies were included in the review, all of which were prospective randomized controlled trials. A total of 1,145 patients were included across all five studies. Among these, 577 patients were randomized to receive ablation, and 568 patients were randomized to receive AAD. The duration of follow-up ranged from 1 year [17–19] to 2 years [20,21]. The selection criteria were similar in that only those patients were considered who had recent onset of AF and were receiving ablation or AAD as first-line treatment. Among the ablation group, there were 392 (67.9%) males and 392 (69.0%) males in the AAD group. None of the coronary artery disease (CAD) risk factors were significantly different across both groups. The AF was characterized as paroxysmal across all studies.

Key outcome measures are summarized in Table 1. The primary outcome was the recurrence of any AF within 1 [17–19] or 2 [20,21] years of the randomization to receive either ablation or AAD. Recurrence of any AF within one year was 111 (30.4%) patients among those who received ablation therapy. In the same period, the recurrence of any AF was noted in 242 (42.6%) patients who received AAD. In the two years, the recurrence of any AF was present in 58 (27.4%) patients who received ablation and 87 (41.6%) patients who received AAD. The health-related quality of life was significantly higher in the ablation group across two studies that assessed it [20,21]. Asymptomatic AF was present in 18 (9.8%) patients who received ablation and 30 (28.8%) patients who received AAD.

Overall, the studies compared the frequency of recurrence of any AF among patients who were treatment-naïve and who were randomized to receive either ablation or AAD. The recurrence rate was significantly higher among patients who received AAD at 1-year and 2-year follow-ups. The HR-QoL was significantly better in the patients who received ablation therapy. The incidence of serious adverse events was 14 (6.4%) in the ablation group and 9 (4.3%) in the AAD group.

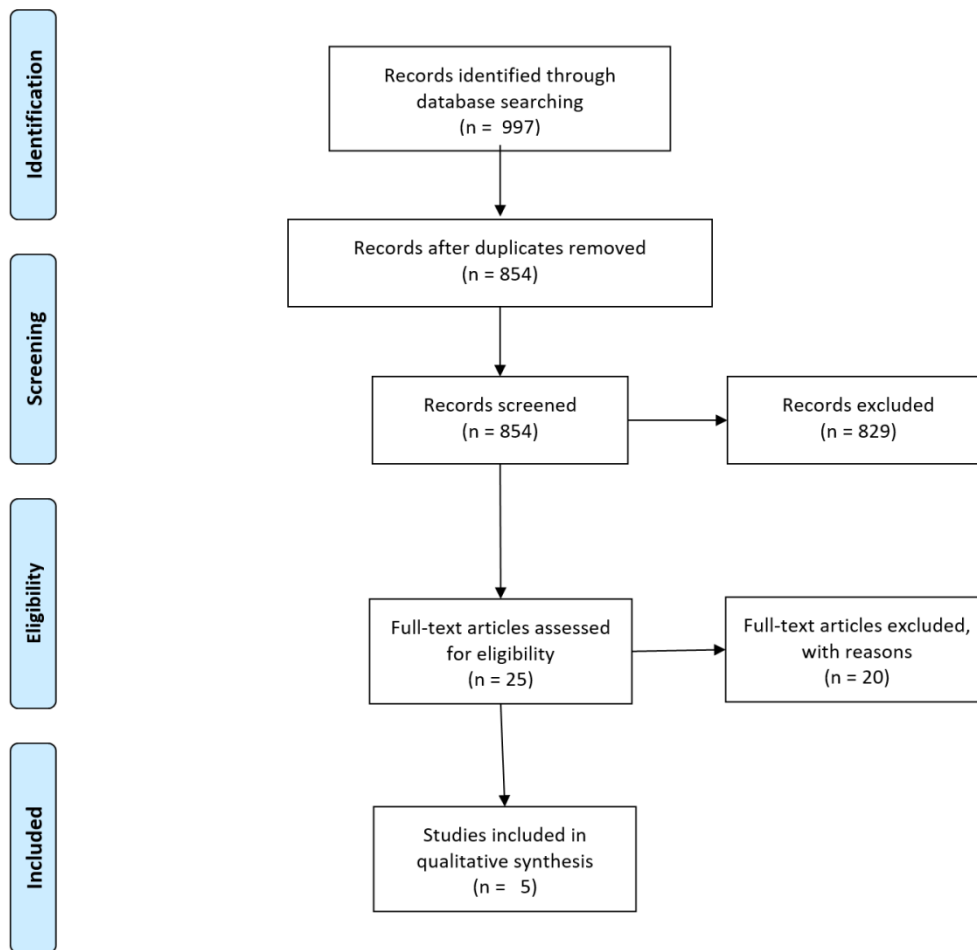
**Table 1. Key characteristics of the included studies in this review**

Variables	Walfridsson et al. [20]	Morillo et al. [21]	Andrade et al. [17]	Wazni et al. [18]	Kuniss et al. [19]
Study type	Prospective RCT	Prospective RCT	Prospective RCT	Prospective RCT	Prospective RCT
Sample size (N)	294	127	303	203	218
Treatment arms	PVI using radiofrequency ablation (n=146) and AAD (n=148)	PVI using radiofrequency ablation (n=66) and AAD (n=61)	PVI using cryo-balloon (n=154) and AAD (n=149)	PVI using cryo-balloon (n=104) and AAD (n=99)	PVI using cryo-balloon (n=107) and AAD (n=111)
Follow-up	2 years	2 years	1 year	1 year	1 year
Monitoring method	7-day Holter-monitoring	Transtelephonic monitoring, 12-lead ECG, Holter, or rhythm strips	Implantable cardiac monitor	12-lead ECG	7-day Holter monitoring and 12-lead ECG
Selection criteria	Patients aged <70 years who experienced at least two episodes of documented AF within the previous 6 months and who have not received AAD	Patients aged 18-75 years who experienced recurrent symptomatic AF $\leq$ 4 episodes within the previous 6 months and who have not been treated with AAD	Patients aged >18 years who had symptomatic AF and at least one episode of AF detected on ECG within 24 hours before randomization	Patients aged 18-80 years who had AF and not received AAD	Patients aged 18-75 years who had recurrent symptomatic AF and who had not received class I or III AAD > 48 hours
Male (n, %); PVI and AAD group	100/146 (68.0%) and 106/148 (72.0%)	51/66 (77.3%) and 45/61 (73.8%)	102/154 (68.5%) and 112/149 (72.7%)	63/104 (61.0%) and 57/99 (58.0%)	76/107 (71.0%) and 72/111 (64.9%)
Mean age (SD), years; PVI and AAD group	56 (9) and 54 (10)	56.3 (9.3) and 54.3 (11.7)	59.5 (10.6) and 57.7 (12.3)	60.4 (11.2) and 61.6 (11.2)	50.5 (13.1) and 54.1 (13.4)
Characteristics of AF; PVI and AAD group	NA	Mean AF episodes in the last 6 months – PVI: 47.4 (SD: 97.9) and AAD: 33 (SD: 48.7)	Median AF episodes/month – PVI: 3 (1-10) and AAD: 3 (1-10)	Time since onset (years) – PVI: 1.3 (SD: 2.5) and AAD: 1.3 (SD: 2.3)	Time since onset (years) – PVI: 0.7 (1.5) and AAD: 0.8 (2.1)
Type of atrial fibrillation	Paroxysmal	Paroxysmal	Paroxysmal	Paroxysmal	Paroxysmal
CAD risk factors; PVI and AAD group	CAD: 6/146 (4%) and 2/148 (1%); Hypertension: 43/146	CAD: 6/66 (9.1%) and 2/61 (3.3%); Hypertension: 28/66	Hypertension: 57/154 (37.0%) and 55/149 (36.9%); Ischemic heart	CAD: 13/104 (12%) and 12/99 (12%); Hypertension:	CAD: 2/107 (1.9%) and 1/111 (0.9%); Hypertension: 33/107

Variables	Walfridsson et al. [20]	Morillo et al. [21]	Andrade et al. [17]	Wazni et al. [18]	Kuniss et al. [19]
	(29%) and 53/148 (39%); Diabetes mellitus: 6/146 (4%) and 10/148 (7%); Chronic lung disease: 8/146 (5%) and 6/148 (4%); Thyroid disease: 10/146 (7%) and 10/148 (7%)	(42.4%) and 25/61 (41.0%); Diabetes mellitus: 1/66 (1.5%) and 4/61 (6.6%)	disease: 12/154 (7.8%) and 7/149 (4.7%); Sleep apnea: 32/154 (20.8%) and 32/149 (21.5%); Stroke or TIA: 4/154 (2.6%) and 5/149 (3.4%)	58/104 (56%) and 57/99 (58%); Diabetes: 15/104 (14%) and 17/99 (17%); Chronic lung disease: 5/104 (5%) and 6/99 (6%); Sleep apnea: 26/104 (25%) and 20/99 (20%)	(30.8%) and 40/111 (36.0%); Diabetes: 1/107 (0.9%) and 4/111 (3.6%); Hyperlipidemia: 23/107 (21.5%) and 25/111 (22.5%)
Mean left ventricular ejection fraction (SD), %; PVI and AAD group	NA	61.4 (4.8) and 60.8 (7.0)	59.6 (7.0) and 59.8 (7.6)	60.9 (6.0) and 61.1 (5.9)	62.8 (5.4) and 63.7 (5.4)
Mean left atrial size (SD), cm; PVI and AAD group	4.0 (6.0) and 4.0 (5.0)	4.0 (0.5) and 4.3 (0.5)	4.0 (0.5) and 3.8 (0.7)	3.9 (5.7) and 3.8 (5.4)	4.7 (8.2) and 4.8 (6.3)
Outcomes	Recurrence of any AF, symptomatic AF, and QoL	Time to the first recurrence of any AF, repeated episodes, and QoL	Recurrence of any AF, performance of repeat ablation, first recurrence of symptomatic atrial tachyarrhythmia, and QoL	Recurrence of any AF	Recurrence of any AF
Primary outcome	Recurrence of any AF – PVI: 22/146 (15%); AAD: 43/148 (29%)	Recurrence of any AF – PVI: 36/66 (54.5%); AAD: 44/61 (72.1%)	Recurrence of any AF – PVI: 66/154 (42.9%); AAD: 101/149 (67.8%)	Recurrence of any AF – PVI: 26/104 (25.4%); AAD: 54/99 (55.0%)	Recurrence of any AF – PVI: 19/107 (17.8%); AAD: 36/111 (32.4%)
Secondary outcome(s)	HRQoL improvement was more pronounced in the PVI group. Asymptomatic AF was present in 12/122 (55%) of the PVI group and 19/43 (44%) of the AAD	HRQoL improvement was more pronounced in the PVI group. Asymptomatic AF was present in 6/61 (9%) of the PVI group and 11/61 (18%) of the AAD group. Serious events in	Recurrence of symptomatic AF was 17/154 (11%) in the PVI group and 39/149 (26.2%) in the AAD group. Serious adverse events in 5/154 (3.2%) of the PVI group: phrenic	NA	The incidence rate of symptomatic palpitations was lower in the PVI (7.61 days/year) group than in the AAD (18.9 days/year) group

Variables	Walfridsson et al. [20]	Morillo et al. [21]	Andrade et al. [17]	Wazni et al. [18]	Kuniss et al. [19]
group		6/66 (13.6%) of the PVI group: tamponade (4/66), severe pulmonary vein stenosis (1/66), bradycardia leading to pacemaker insertion (1/66); 3/61 (4.9%) of the AAD group: atrial flutter with 1:1 atrioventricular conduction (1/61), syncope (2/61)	nerve palsy (3/154) and symptomatic bradycardia requiring pacemaker (2/154); 6/149 (4.0%) of the AAD group: wide-complex tachycardia (2/154), syncope (1/154), heart failure (1/154), and symptomatic bradycardia requiring pacemaker (2/154)		

AAD: Anti-arrhythmic drugs; AF: Atrial fibrillation; CAD: Coronary artery disease; NA: Not available; PVI: Pulmonary vein isolation; RCT: Randomized controlled trial; SD: Standard deviation



**Fig. 1. PRISMA flow diagram for this study**

#### 4. DISCUSSION

In this systematic review of 5 RCTs, we reviewed the efficacy and safety outcomes of ablation versus AAD as first-line therapy among 1,145 symptomatic AF patients. We found that ablation, either by cryoballoon or radiofrequency-focused pulmonary vein isolation, had a significantly lower recurrence rate of any atrial tachyarrhythmias when administered in treatment-naïve patients. These findings were similar in both 1-year and 2-year follow-up periods. There were comparably lower serious adverse events in the ablation group, and the health-related quality of life was higher in the ablation group. There were lower incidence rates of symptomatic AF among patients who received ablation therapy. Our study focuses on the clinical outcomes of ablation versus AAD in recent trials.

Both radiofrequency ablation (RFA) and cryoballoon ablation (CBA) are considered safe

options for the treatment of AF [22,23]. The underlying triggers for paroxysmal AF are assumed to originate in the pulmonary and thoracic veins [24,25]. Therefore, the role of CBA which electrically targets the pulmonary vein has been considered promising [26]. However, ablations are only considered if AAD treatment has been unsuccessful at preventing recurrence [27]. The efficacy of ablation remains stronger when considered early, or the AF may become refractory [28]. Also, the time-to-ablation has been associated with better patient outcomes [29]. Previous data [30,31] and our findings promote early ablation treatment with more favorable results for AF management.

#### 5. CONCLUSION

The current systematic review reported the evidence on the efficacy and safety of catheter ablation and antiarrhythmic drugs as treatment for symptomatic AF in treatment-naïve individuals. In our findings, all five studies found

that the recurrence rate of any AF was significantly lower in the group that received catheter ablation. This was not associated with an increased risk of serious adverse events and was supported by a comparatively higher health-related quality of life in this group.

## 6. LIMITATIONS

There are certain limitations to this study. The outcome measures were variable across the included studies. There were differences in the method of monitoring the recurrence and different time points for follow-up ranging from 1-2 years. While not the focus of the review, different classes of AADs, including I or III, were used. This study focused on paroxysmal AF, and the findings cannot be generalized to those with persistent AF. Finally, the technique for ablation is dependent on the interoperator variability. Regardless, the strengths of this study are that the studies were RCTs, and all the studies had reported superiority of ablation to AAD in the prevention of recurrence of paroxysmal AF without a higher risk of adverse events.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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