







ORIGINAL ARTICLE

Radiofrequency or cryoablation or medical therapy for paroxysmal atrial fibrillation: An indirect comparison of effectiveness

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Abstract

Background: Paroxysmal atrial fibrillation (PAF) is commonly treated with pharmacological therapies, but these may be insufficient for symptom control. Radiofrequency and cryoballoon ablation have emerged as alternative strategies. This study aimed to compare the efficacy of cryoballoon ablation, radiofrequency ablation, and anti-arrhythmic drugs as initial therapies for symptomatic PAF based on randomized trial data.

Methods: Data were extracted from randomized trials, and individual patient data were reconstructed from Kaplan–Meier curves using artificial intelligence techniques. Time-to-event analysis was performed to evaluate arrhythmia recurrence, with hazard ratios (HRs) as the primary measure of efficacy. A heterogeneity analysis was conducted to assess variability between studies.

Results: Five randomized trials were included in the analysis. Significant between-trial heterogeneity was observed. Both cryoballoon ablation (HR 0.48; 95% CI: 0.36–0.63; $p < .001$) and radiofrequency ablation (HR 0.54; 95% CI: 0.37–0.80; $p = .002$) demonstrated superior efficacy compared to anti-arrhythmic drug therapy in reducing arrhythmia recurrence.

Conclusions: Cryoballoon and radiofrequency ablation are more effective than anti-arrhythmic drugs for initial therapy in symptomatic PAF. These findings support the use of ablation techniques as preferred interventions in this patient population.

KEYWORDS

cryoballoon ablation, indirect comparison, paroxysmal atrial fibrillation, radiofrequency ablation

1 | INTRODUCTION

Atrial fibrillation (AF) is the most common type of cardiac arrhythmia and is linked to a higher risk of stroke, heart failure, and sudden death.¹ Patients who experience episodes of AF that resolve spontaneously or with treatment within 7 days are diagnosed with paroxysmal AF (PAF). The primary treatments for controlling heart rhythm in these patients are anti-arrhythmic drugs (AADs) and catheter ablation (CA).

Radiofrequency (RF) catheter ablation is a commonly used thermal-based method that has been shown to improve heart rhythm outcomes more effectively than medical therapy in patients with PAF.² The beneficial effects of contact force (CF) measurement on procedure and RF times, as well as recurrence rates, have led to the widespread adoption of irrigated CF-sensing catheters.

Another technique is cryoballoon ablation (CBA) that uses freezing temperatures to trigger a specific tissue response. The first-generation cryoballoon demonstrated greater efficacy than AADs in randomized clinical trials (RCTs).³ Introduced in 2012, the second-generation cryoballoon features a modified refrigerant injection system with eight jets positioned more distally on the balloon.

Data on first-line treatment for patients with symptomatic PAF are scarce. This study indirectly compared the efficacy of CBA versus RFA versus AADs as initial therapy for symptomatic PAF. Several randomized trials have proposed two types of thermal ablation (RF or CBA) as first-line treatment for this condition.^{4–8} Herein, we conducted the present comparative analysis using a new artificial intelligence (AI) technique called the “IPDfromKM” method or the Shiny method⁹ to review the current literature.

The IPDfromKM method is an innovative AI tool that reconstructs individual patient data from the graph of Kaplan–Meier (KM) curves, facilitating cross-study comparisons based on reconstructed patient data.^{10,11} This method presents an easy-to-understand summary of the results by generating a unique multi-curve plot containing the KM curves of reconstructed patients. The treatments are compared statistically using standard parameters such as the hazard ratio (HR) and confidence interval (CI). An advantage of the IPDfromKM analysis is that the value of the HR is influenced by the time course of the curves projected over the entire follow-up period. This report provides an original comparative analysis between medical therapy, radiofrequency, or cryoballoon ablation for paroxysmal atrial fibrillation based on comparative trials published in recent years.

2 | MATERIALS AND METHODS

2.1 | Study design and literature search

We conducted a PubMed literature search (last search run on 14 July 2024) to identify RCTs eligible for this analysis. The search term “(atrial AND fibrillation AND (radiofrequency OR cryo* OR medical therapy))” was employed in combination with the filter “randomized controlled trials.” Results were reported according to the Preferred

Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement.¹² Additionally, we searched the Cochrane Library for any recent systematic reviews on this subject, the [ClinicalTrials.gov](https://www.clinicaltrials.gov) database, and the websites of the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA). The keyword “paroxysmal atrial fibrillation” was also used for these additional searches.

Our analysis included trials that met the following criteria: (a) previously untreated patients with PAF; (b) randomized design; (c) evaluation of at least one treatment involving AADs, RF, or CBA; (d) determination of atrial fibrillation recurrence using a KM curve with follow-up of at least 12 months. The endpoint of our analysis was arrhythmia recurrence. No restrictions were employed in terms of physical fitness or age of the population under examination. Studies reported in duplicate publications were included only once. For each trial, we extracted the basic information needed for our analysis.

In analyzing each treatment arm of each trial, patient-level data were reconstructed from the KM curve using the IPDfromKM method. This method was run through its web-based version; all the remaining statistical analyses were performed according to specific packages designed for the R-platform.^{10,11} Heterogeneity was assessed through the likelihood ratio test and Wald's test. Results were presented using hazard ratio (HR), medians along with their 95% confidence intervals (CI). Finally, the information on serious adverse events (SAEs) was collected from included trials.

3 | RESULTS

3.1 | Literature search and selection of included trials

Our literature search (see PRISMA schematic in [Figure S1](#) in the Supplementary material) extracted a total of 59 RCTs from which we identified five eligible RCTs.^{4–8} The type of atrial fibrillation was paroxysmal in all five studies. [Table 1](#) shows the main characteristics of the five trials included in our analysis.

3.2 | Heterogeneity assessment

[Figure 1](#) shows assessment of between-trial heterogeneity, which was performed for medical therapy (Panel A, 5 study arms) since this treatment arm was present in all five included studies. These five curves were based on reconstructed patients generated by the IPDfromKM method. A significant level of heterogeneity was found in these five KM curves. The detailed results of this analysis were as follows: likelihood ratio test = 38.36 on 4 df, $p < .001$; Wald test = 34.27 on 4 df, $p < .001$. The high heterogeneity we found likely depends on the baseline characteristics of the patients enrolled in the studies; indeed, the studies by Andrade et al.⁴ and Wazni et al.⁵ enrolled patients with a higher rate of severe cardiac condition compared to the other studies.

TABLE 1 Main characteristics of the five controlled trials. The endpoint was arrhythmia recurrence.

Data-set	Cohort	Inclusion criteria	Mean age (years) and gender	t* (mos)	No. of patients	Number of recurrences (mos)
Andrade et al. ⁴	1. Cryoballoon	Previously untreated with antiarrhythmic drugs	57.7; male, 72.7%	12	154	66
	2. Medical therapy		59.5; male 68.5%		149	101
Wazni et al. ⁵	3. Cryoballoon	Previously untreated with antiarrhythmic drugs	60.4; male, 61%	12	104	26
	4. Medical therapy		61.6; male, 58%		99	51
Morillo et al. ⁶	5. Radiofrequency	Previously untreated with antiarrhythmic drugs	56.3; male, 77.3%	12	66	36
	6. Medical therapy		54.3; male, 73.8%		61	44
Wazni et al. ⁷	7. Radiofrequency	Previously untreated with antiarrhythmic drugs	53 ^a	12	32	4
	8. Medical therapy		54 ^a		35	21
Kuniss et al. ⁸	9. Cryoballoon	Previously untreated with antiarrhythmic drugs	50.5; male, 71.0%	12	107	16
	10. Medical therapy		54.1; male, 64.9%		111	33

^aIn these two cases, the number of events was not explicitly reported in the original article; therefore, these two values of 53 and 54 events were estimated by the IPDfromKM program through a specific option of the software.

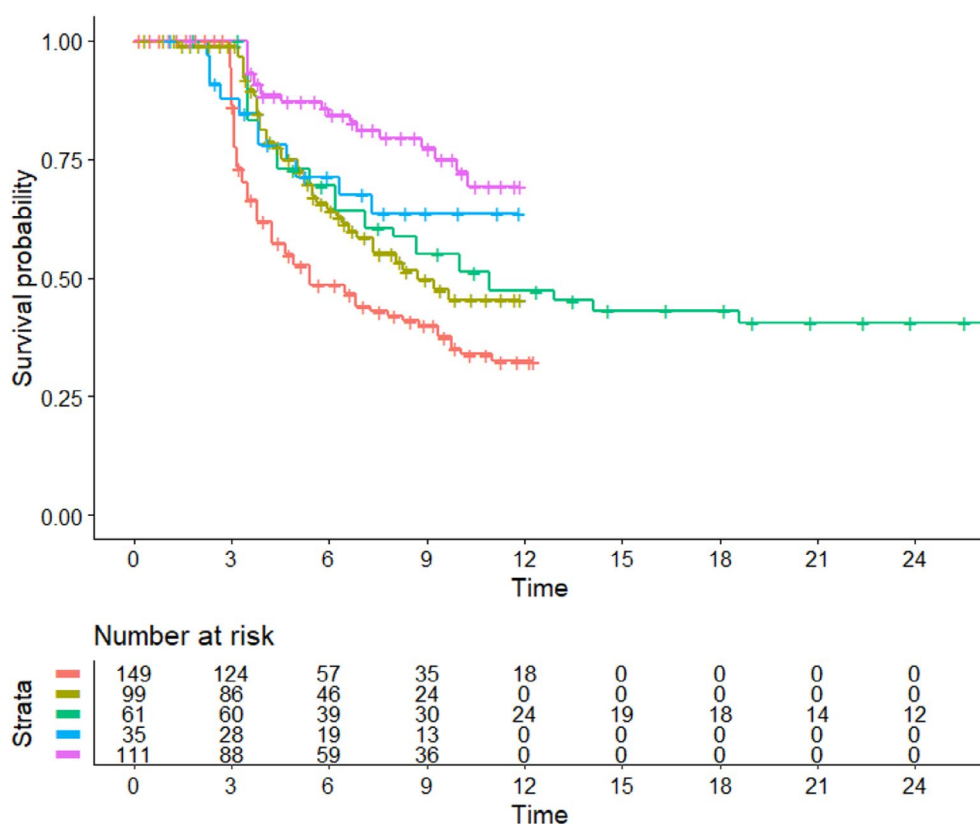


FIGURE 1 Analysis of the five included trials: assessment of heterogeneity for control groups treated with medical therapy. Legends: Andrade et al.⁴ (n = 149) in red; Wazni et al.⁵ (n = 99) in military green; Morillo et al.⁶ (n = 61) in light green; Wazni et al.⁷ (n = 35) in blue; Kuniss et al.⁸ (n = 111) in purple. Endpoint, arrhythmia recurrence. Time in months.

3.3 | Analysis of recurrence-free curves

Also this analysis was based on reconstructed patients generated by the IPDfromKM method. The analysis yielded the results shown in Figure 2. Patients undergoing cryoablation (HR 0.48; 95% CI: 0.36–0.63; $p < .001$) or radiofrequency ablation (HR 0.54; 95% CI: 0.37–0.80; $p = .002$) demonstrated superiority in comparison with medical therapy.

3.4 | Serious adverse events

Table S1 in the Supplementary Appendix summarizes the information on SAEs reported in the five included trials. These results, which, as expected, show a lower incidence of SAEs in patients treated with antiarrhythmic drugs, are influenced by the different definitions of SAEs in the five trials.

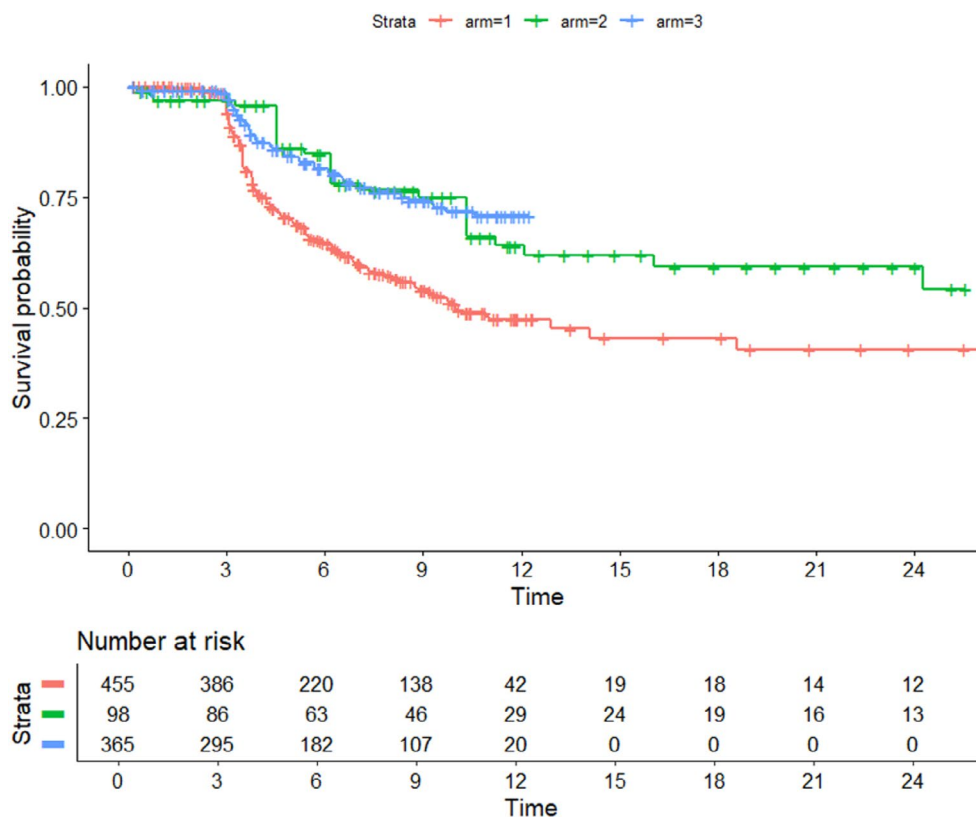


FIGURE 2 Application of the IPD from KM method: results in untreated patients. In red, patients from five trials undergoing medical therapy ($n=455$); in green, Patients from two trials undergoing radiofrequency ($n=98$); in blue, Patients from the three trials undergoing cryoablation ($n=365$). Time in months.

4 | DISCUSSION

Our results clearly indicated that radiofrequency and cryoballoon ablation techniques fared better than medical therapy as first-line treatment in patients with paroxysmal atrial fibrillation. While a major advantage of our study is the accurate management of recurrence-free data resulting from the use of the IPDfromKM method, an important limitation is that it is focused exclusively on efficacy. For this reason, in Table S1, we have summarized the main information on SAEs reported in the five included trials.

Our results on efficacy align with the recent consensus document from the most prominent scientific societies specializing in cardiac arrhythmias.¹³ In recent years, it is well known that a new ablation method called pulsed-field ablation has been developed for the treatment of PAF in drug-resistant patients. It will be interesting to determine whether this new technique proves superior in terms of efficacy when used as a first-line treatment.¹⁴

The limitations intrinsic to indirect comparisons are well known¹⁵ and are exemplified in this study. Furthermore, our research considered studies published over a span of nearly two decades, ranging from 2005 to 2024, and this might include some unidentified biases. For example, the efficacy of radiofrequency reported in our analysis may be somewhat biased because the overall therapeutic context for AF was likely to have been worse several years ago. However, our

heterogeneity analysis focused on the five control groups (Figure 1) did not confirm this hypothesis, because the study published by Wazni et al.⁷ in 2005 did not report worse outcomes for drug-treated patients compared with those of the other four RCTs.

Another limitation of our study is that our literature search was limited to RCTs and excluded registry data, which may provide valuable information on patients undergoing first-line catheter ablation. Furthermore, several randomized trials available in the literature did not meet the inclusion criteria of our study protocol. In addition, limiting our analysis to a single clinical endpoint may not fully reflect the overall effectiveness of a specific therapy, as complication rates may also play a role in these comparisons; however, our analysis focusing on SAEs did not identify an important role for this information for the purpose of our comparative analysis. Finally, the sample sizes of the selected RCTs were relatively small, especially in the RF ablation trials.

AUTHOR CONTRIBUTIONS

A Messori was responsible for study conception and design; L Cancanelli and R Brunoro were responsible for the acquisition of data; M Rivano and L Di Spazio were responsible for data analysis and drafting; R Brunoro, CN Fasano Celentano, D Mengato, and A Messori were responsible for data quality assurance, revision of the manuscript, and final approval of the version to be published.

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CONFLICT OF INTEREST STATEMENT

All authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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