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Short Communication

Medical therapy, radiofrequency ablation or cryoballoon ablation as first-line treatment for paroxysmal atrial fibrillation: interpreting efficacy through restricted mean survival time and network meta-analysis

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When multiple treatments are available, network meta-analysis can evaluate data to rank the relative effectiveness. We applied this approach to first-line treatments for paroxysmal atrial fibrillation (medical therapy, radiofrequency ablation or cryoballoon ablation). Individual trials were analysed based on the restricted mean survival time (RMST). Randomised controlled trials (RCT) assessing first-line treatments for paroxysmal atrial fibrillation were referenced from PubMed and the websites of regulatory agencies. The primary endpoint was atrial fibrillation recurrence-free survival at 12 months. The treatments assessed for their relative effectiveness were medical therapy, radiofrequency ablation and cryoballoon ablation. Individual trials were examined based on RMST. A Bayesian network meta-analysis was conducted to comparatively evaluate these treatments. Five trials were included in the analysis: two compared radiofrequency with medical treatment and three cryoballoon ablation with medical treatment. The indirect comparison of radiofrequency ablation vs cryoballoon ablation was assessed in the absence of RCTs. Differences in RMST (with 95% credible intervals) were estimated for all binary comparisons (direct or indirect). Radiofrequency and cryoballoon ablation showed significantly increased effectiveness compared with medical treatment. In the indirect comparison, radiofrequency showed a non-significant advantage over cryoballoon ablation. The ranking of effectiveness was as follows: (1) radiofrequency; (2) cryoballoon ablation; (3) medical treatment. In conclusion, we found that radiofrequency was the most effective treatment for paroxysmal atrial fibrillation according to a Bayesian probabilistic model.

Keywords

Meta-analysis; Paroxysmal atrial fibrillation; Restricted mean survival time; Cryoablation; Radiofrequency

1. Introduction

The literature on the effectiveness of catheter ablation for paroxysmal atrial fibrillation (PAF) continues to evolve [1–3]. Randomised trials on cryoablation have focused on first-line treatment for this disease condition [4–9]. The effectiveness of cryoballoon ablation as a first line therapy has been investigated in three randomized controlled trials (RCTs) [4, 5, 9], and several observational studies [6–8].

The restricted mean survival time (RMST) is increasingly recognised to be an excellent methodological option to evaluate survival and event-free survival amongst various therapies [10]. Therefore, we sought to comparatively evaluate the effectiveness of medical therapy, radiofrequency ablation and cryoballoon ablation as a first line therapy for PAF and to rank them according to their effectiveness using RMST and a network meta-analysis.

2. Methods

We conducted a PubMed literature search (last query run on May 22, 2021) to identify RCTs for this analysis. A search term "(atrial AND fibrillation AND (radiofrequency OR cryo*))" was employed in combination with the filter "randomised controlled trials". Results were reported according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement [11]. We also searched the Cochrane Library for any recent systematic reviews on this subject, the ClinicalTrials.gov data-base, and the websites of European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA). The keyword "paroxysmal atrial fibrillation" was also employed for these additional searches.

Our analysis included the trials that met the following criteria: (a) previously untreated patients with PAF; (b) evaluation of at least one treatment involving medical therapy, radiofrequency and cryoablation; (c) determination of atrial fibrillation recurrence using a Kaplan-Meier curve with follow up of at least 12 months. No restrictions were employed in terms of physical fitness or age of the study population. Randomised studies reported in duplicate publications were included once only.

For each trial, we extracted the basic information needed for our analysis. Information on disease condition at baseline was also recorded.

In analysing each treatment arm of each trial, patient-level data were reconstructed from the Kaplan-Meier curve, to determine RMST and mean lifetime survival (MLS) as previously described (procedures designed for the R-platform) [12, 13].

Our network meta-analysis (NETMA) was carried out according to a standard Bayesian method [14]. This approach is advantageous because all treatments included in the comparisons are incorporated into a single statistical model in contrast to other approaches in which there are as many separate analyses as the number of comparisons being studied. Both fixed-effect and random-effect models were tested; the model for our primary analysis was chosen based on deviance information criterion (DIC). Results were presented through credible intervals (CrIs) of differences in RMST. Iconographic presentation of results was based on a figure that reports network geometry along with the results of the analysis [15–17]. Finally, rankings were determined according to the surface under the cumulative ranking area (SUCRA) method [18].

The quality of evidence for the 5 studies was assessed according to GRADE's algorithm [19].

3. Results

Our literature search (see PRISMA schematic in **Supplementary Fig. 1** of our preprint [20]) extracted a total of 293 RCTs from which we identified 6 eligible RCTs [4–9]. Of these, one [9] was excluded because no Kaplan-Meier curve was reported, whereas five [4–8] met our inclusion criteria and were included in our analysis. These 5 randomized studies were rated as having a high level quality of evidence. The type of atrial fibrillation was paroxysmal in all 5 studies. All subjects gave their informed consent for inclusion before they participated in each study.

In conducting our NETMA, we separately ran the fixed-effect and the random-effect models. According to the deviance information criterion (DIC), the fixed-effect model showed a better fit.

Table 1 (Ref. [4–8]) shows the values of RMST estimated from these trials (with milestone set at 12 months) along with differences in RMST between treatment group and controls. Although the values of MLS showed wide 95% CIs (see **Supplementary Table 1** in our preprint [20]), examining their values (see Table 1) is worthwhile irrespective of their statistical variations.

Fig. 1A (Ref. [4–8, 15–17]) shows the geometry of direct and indirect comparisons and also the results of our NETMA. With respect to atrial fibrillation recurrence (from 0 to 12 months), radiofrequency ablation and cryoballoon ablation showed a higher effectiveness than medical treatment, both at significant levels. These two catheter ablation techniques determined a gain in recurrence-free survival of more than 2 months compared with medical therapy. This is remarkable considering that the milestone of our analysis was set at 12 months. The indirect comparison showed no significant difference between the two ablative techniques, resulting only in a numerical advantage in favour of radiofrequency.

According to these findings, in our probabilistic analysis radiofrequency ranked first, cryoballoon ablation second and medical therapy third. Rankings appeared to be robust according to probabilistic criteria, as confirmed by the SUCRA (surface under the cumulative ranking area) histogram of rankings (Fig. 1B).

4. Discussion

Our results clearly indicated that the two ablation techniques fared better than medical therapy. Furthermore, in the indirect comparison between cryoballon ablation and radiofrequency no evidence for different effectiveness was found from these 5 RCTs. As more follow-up accumulates, it will be worthwhile to update the analysis of these 5 RCTs based on a RMST milestone at more than 12 months. It should be noted that our study is one of the first examples where NETMA has been combined with RMST as an outcome measure (e.g., see Petit *et al.* [21]).

The limitations intrinsic to indirect comparisons are well known [18], and are exemplified in this study. In particular, comparing three cryoballoon ablation studies published in 2021 with two radiofrequency ablation studies published in 2014 and 2005 might include some unidentified biases. For example, the effectiveness of radiofrequency reported in our analysis might be somewhat biased because, several years ago, the context of ablation of atrial fibrillation likely had a worst overall performance. However, despite this (potential) disadvantage, radiofrequency has ranked first in our analysis, and so its "true" performance could even be better than shown by our findings. Another limitation is that our study protocol was exclusively aimed at RCTs, and excluded registry data, where useful information on patients subjected to first-line catheter ablation may be available. Furthermore, several randomised studies available from the literature did not meet the inclusion criteria set by our study protocol, mainly because these studies employed the endovascular treatments as second line; in one case, patients treated as first-line therapy did not represent 100% of the population, even though a direct comparison was made between cryoballoon ablation and radiofrequency [22]. This, however, emphasises the homogeneity of the 5 trials included in our analysis Limiting our analysis to a single clinical end-point may not reflect the overall effectiveness of a specific therapy, since the rate of complications can also have a role in these comparisons. Amongst the 5 RCTs, the study published in 2005 by Wazni *et al.* [7] was considerably older compared to other studies. Finally, the sample size of the RCTs selected, especially in RF ablation studies, was small.

In conclusion, based on the limitations of the existing data, a prospective, randomized trial is necessary to better determine the clinical efficacy of radiofrequency and cryoballoon ablation at first line therapy for PAF.

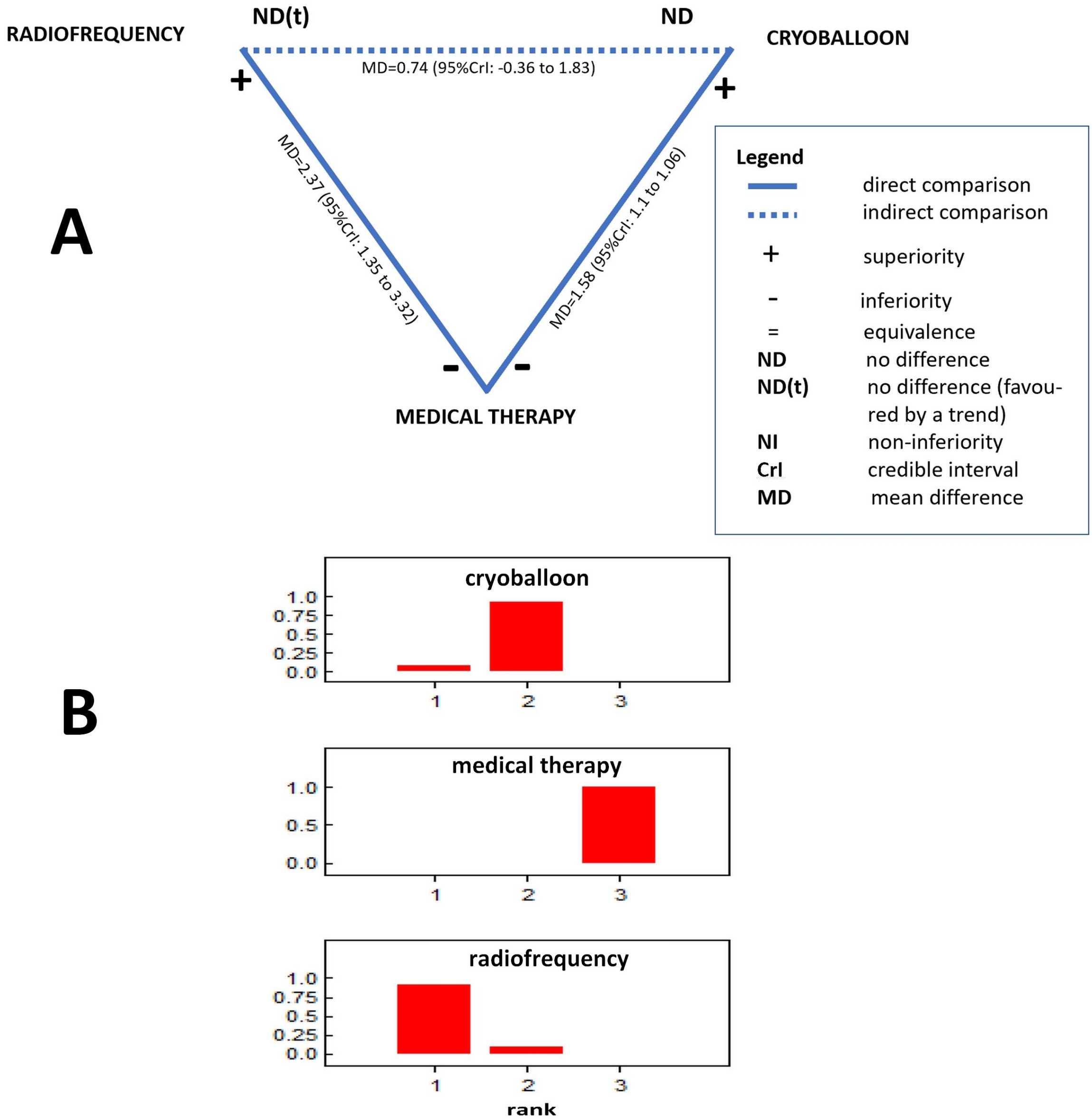

Fig. 1. Network meta-analysis. (A) Network geometry. The graphical schematization follows the proposal by Fadda *et al.* [15, 16]. Direct comparisons are represented as solid lines and indirect comparisons as dotted lines. The comparisons are based is based on two RCTs (Morillo *et al.* 2014 [6]; Wazni *et al.* 2005 [7]) for radiofrequency vs medical therapy, and three RCTs (Andrade *et al.* 2021 [4]; Wazni *et al.* 2021 [5]; Kuniss *et al.* 2021 [8]) for cryoablation vs medical therapy. (B) Histogram of rankings generated by the Bayesian network meta-analysis. The graphs reflect a total of 60,000 iterations and consist of as many histograms as the treatments (N = 3) included in the analysis. In each panel, the histogram shows the percent distribution of the simulations across ranks 1 (most effective treatment) through 3 (least effective treatment); the y-axis shows probability on a 0 to 1 scale. The overall ranking in effectiveness was the following: (1) radiofrequency; (2) cryoablation; (3) medical therapy.

Table 1. Characteristics of the 10 cohorts and values of RMST estimated from the time-to-event curves (analysis with milestone of 12 mos).

Data-set	Cohort	Mean age (yrs) and gender	t* (mos)	No. of patients	RMST (mos) with 95% confidence interval	Trial-specific gain from 0 to 12 months (mos)	MLS (mos)	Trial-specific lifetime gain (mos)
Andrade *et al.* 2021 [4]	Cryoballoon	57.7 male, 72.7%	12	154	9.36 (8.83 to 9.9)	2.27	20.72	10.8
	Medical therapy[a]	59.5 male, 68.5%		149	7.09 (6.47 to 7.72)		9.92	
Wazni *et al.* 2021 [5]	Cryoballoon	60.4 male, 61%	12	104	10.33 (9.66 to 10.99)	1.64	33.71	22.07
	Medical therapy[b]	61.6 male, 58%		99	8.69 (7.88 to 9.51)		11.64	
Morillo *et al.* 2014 [6]	Radiofrequency	56.3 male, 77.3%	12	66	9.67 (8.89 to 10.44)	1.54	31.15	15.18
	Medical therapy[c]	54.3 male, 73.8%		61	8.13 (7.24 to 9.02)		15.97	
Wazni *et al.* 2005 [7]	Radiofrequency	53§	12	33	10.98 (10.03 to 11.93)	3.71	not computable†	not computable
	Medical therapy[d]	54§		37	7.27 (5.99 to 8.54)		not computable†	
Kuniss *et al.* 2021 [8]	Cryoballoon	50.5 male, 71.0%	12	107	16.74 (16.07 to 17.41)	1.49	66.3	39.55
	Medical therapy[e]	54.1 male, 64.9%	12	111	15.25 (14.38 to 16.12)		26.75	

Abbreviations: t*, milestone; mos, months; RMST, restricted mean survival time; MLS, mean lifetime survival (estimated through Weibull extrapolation).

† The fit based on Weibull function performed under R-platform failed because of insufficient information in the Kaplan-Meier curve. § No information on gender.

[a] Flecainide (median dose, 200 mg per day) was the most frequently prescribed antiarrhythmic drug (76.5%). [b] Flecainide was the most frequently prescribed antiarrhythmic drug (61.7%). [c] Flecainide was the most frequently prescribed antiarrhythmic drug (69%). [d] 62% received beta-blocker therapy. [e] Flecainide was the most frequently prescribed antiarrhythmic drug (60.4%).

Author contributions

Conceptualization, AM, LB, EF, and ST; methodology, AM and ST; software, AM; validation, AM and LB; resources, AM; data curation, LB; writing—original draft preparation, AM, ST, and LB; writing—review and editing, AM and ST. All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

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Conflict of interest

The authors declare no conflict of interest.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at https://rcm.imrpress.com/EN/10.31083/j.rcm2203067.

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