Cryoablation vs. Anti-Arrhythmic drug therapy as a first line treatment in Atrial fibrillation (meta-analysis and systematic review)

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April 16, 2024

Abstract

Intro: Atrial fibrillation (AF) is the most frequently diagnosed arrhythmia in practice. Current guidelines on management of AF suggest that patients should be treated with antiarrhythmic drugs (AAD) as first-line therapy, our meta-analysis aims to assess the benefit of using of Cryoablation as a first line therapy for people with atrial fibrillation. Methods: We conducted an electronic search using Medline, Embase, CINAHL and google scholar along with other clinical trial registries. Results: 2 studies out of 9,244 studies fit our eligibility criteria. A total of 521 subjects were included in both studies and 4 distinct meta-analyses were performed. In terms of recurrence CA was superior to AAD with a RR of 0.6. For serious adverse events CA was also superior to AAD with a RR of 0.66 and for treatment related SAE the results were insignificant. Conclusion: CA proved to be superior in terms of recurrence and adverse effects versus AAD.

Introduction:

Atrial fibrillation (AF) is the most frequently diagnosed arrhythmia in practice. AF is also the most heavily associated arrhythmia with poor outcomes, such as morbidity, mortality and poor quality of life (1,2). Current guidelines on management of AF suggest that patients should be treated with antiarrhythmic drugs (AAD) as first-line therapy, but if a patient becomes refractory to AAD, catheter ablation (CA) with pulmonary vein isolation is recommended as the next in line treatment (3). The two methods of CA being used today are radiofrequency (RF) CA and cryoablation (4).

Contrary to the current recommendations, three popular randomized control trials (RCT's) (RAAFT-1, RAAFT-2 and MANTRA-PAF) have shown that when comparing RF CA to AAD, RF CA had more favorable outcomes in younger patient populations, when used as first-line therapy; however, these patients were more likely to develop adverse effects, including pericardial effusion with tamponade (5,6,7). The more recent CABANA RCT showed that the risk of death, disabling stroke, serious bleeding or cardiac arrest were similar in AF patients treated initially with either AAD or RF CA. However, it did find that AF patients who were initially treated with RF CA, had more favorable outcomes in total mortality, cardiovascular hospitalizations and AF recurrence (8).

FIRE AND ICE was the first trial to compare cryoablation to RF CA in the treatment of refractory AF. The study showed that cryoablation and RF CA did not significantly vary in terms of efficacy (9). However, patients who were treated with cryoablation CA had significantly fewer AF recurrence, and cardiovascular, and all-other-cause re-hospitalizations as compared to patients who received RF CA (10). Moreover, in light of new studies directly assessing the efficacy of cryoablation CA as first-line treatment in comparison to AAD, cryoablation CA had improved ability to reduce the recurrence of AF in a 12-month period, as well as have

relatively low risk of operation-based complications (11,12). Finally, the recent study "CRYO-FIRST" once again showed that Cryoablation CA as first-line therapy displayed significant improvement when compared to AAD's in reducing atrial arrhythmia recurrence in relatively young patients with paroxysmal AF (13).

A recent systematic review studied the previously mentioned RAAFT-1, RAAFT-2 and MANTA-PAF studies along with three studies that utilized cryotherapy (CRYO-FIRST, STOP-AF, and EARLY-AF) as the method of ablation. The results showed significant decrease in recurrence of atrial arrhythmia and hospitalization (14).

This review aims to assess the effectiveness of cryotherapy CA alone as first-line therapy when compared to AAD. This study could contribute to establishing further guidelines on specific first-line treatment for AF.

Material & Methods

Our systematic review is performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (15) checklist for reporting and following the protocol registered a priori on PROSPERO.

Eligibility criteria:

Included studies met the following criteria:

- Studies need to be Randomized controlled trials (RCT) other study designs were excluded.
- Population: patients known to have atrial fibrillation w/o history of antiarrhythmic drug treatment or surgery.
- Intervention and Comparison: Cryoablation and AAD respectively
- Outcome: Recurrence of arrhythmia or any other related morbidity

Studies that did not meet these criteria were excluded. Two investigators used a standardized spreadsheet, based on the inclusion and exclusion criteria, in order to select studies to be included in the review.

Data sources and searches:

We looked at all published and unpublished RCTs of Cryoablation being used as a first line therapy to treat atrial fibrillation. We consulted the head of Saab Medical Library, Dr. Ola El Zein to create a comprehensive search strategy. We applied the search strategy and modified it to fit different official and grey literature databases, as well as RCT registers.

Electronic searches:

We used the following electronic databases for our search:

- MEDLINE, Ovid platform, searched from 1946 to 5 May 2021
- Embase, Ovid platform, searched from 1980 to 5 May 2021
- CINAHL, Ebsco platform, searched from 1961 to 5 May 2021
- Google Scholar, Web platform, searched on 5 May 2021

Searching other resources:

We explored all results relating to the searches "atrial fibrillation" and "cryoablation", through the following RCT registers on 5 May 2021:

- ClinicalTrials.gov
- EU Clinical Trials Register (EU-CTR)
- International Clinical Trial Registry Platform (ICTRP)
- International Standard Randomized Controlled Trial Number Registry (ISRCTN)
- CENTRAL
- UK Clinical Trials Gateway
- WHO International Clinical Trials Registry Platform

Study selection:

Decisions to select retrieved studies for further assessment are based on eligibility criteria. To minimize the chance of including non-relevant studies, two independent, trained researchers (AK and KA) went through the abstracts of every article and excluded the ones they seem unfit the decision to obtain and assess the full text was on whether one reviewer judged the article as fit for our study.

Subsequently, reviewers (AK, KA) conducted a full text review for all studies that passed the abstract screening. In case of conflict a third senior reviewer (MR) was asked to review the articles in question and decide, independent on what previous researchers decided upon. Two investigators used a standardized spreadsheet, based on the inclusion and exclusion criteria, in order to select studies to be included in the review. Reviewers were trained, and the spreadsheet was piloted prior to abstract screening.

Data Extraction:

Two independent reviewers extracted data onto 3 different forms; abstract of relevant data, assess risk of bias, statistical Data.

For the abstract of relevant Data form, extracted data included year of publication, study design, patient entry period, number of patients, population demographics (i.e. age, sex), surgical characteristics (type of cryoablation), drug characteristic (dosage, period and type of AAD), place of intervention and follow up period.

For the assess risk of bias form, we worked according to the Cochrane Collaboration's tool for assessing risk of bias (Higgins 2011), and extracted data relevant to each risk of bias: (16)

- Random sequence generation (selection bias)
- Allocation concealment (selection bias).
- Blinding of participants and personnel (performance bias).
- Blinding of outcome assessment (detection bias).
- Incomplete outcome data (attrition bias).
- Selective reporting (reporting bias).
- Other sources of bias.

Afterwards, we evaluated each risk as high, low, or unclear, as stated by Higgins 2011. Discrepancies were resolved by discussing every risk of bias until consensus was reached. Since our study has a surgical component, blinding was not possible for ethical and practical reasons. Furthermore, our measurement of outcome should not be affected by unblended participants, since they are all objectively measured, for example; morbidity and mortality.

For the statistical data we extracted, the total number of participants in each leg of each study, % of follow up, number of serious adverse events, number of serious adverse events related to trial, recurrence Atrial Fibrillation, Atrial Tachycardia, Atrial Flutter all the data was reported within 1 year of follow up post treatment.

Measures of treatment effect:

For dichotomous outcomes, we calculated a pooled estimate of the treatment effect for each outcome across trials as Risk Ratio (RR) with 95% confidence intervals (CIs). For continuous data, we calculated a pooled estimate of treatment effect by calculating the mean difference (MD) and standard deviation (SD) with corresponding 95% CIs. We used Review Manager software (Revman 5) to calculate the measures of treatment effect.

Unit of analysis issues

We did not intend to include non-standard designs, such as cross-over trials and cluster-RCTs, in this systematic Review. We considered each participant as an individual unit of analysis.

Dealing with missing data

We contacted the authors of the included trials via email for clarification regarding any missing data. We planned to undertake sensitivity analyses to assess the impact of missing data on the quality of the included trials when necessary.

Assessment of heterogeneity

We used the Chi*2 test on N-1 degrees of freedom with a significance level of P less than 0.05, and the IQ statistic to examine the heterogeneity among trials. A guide to interpretation is as follows, as described in the Cochrane Handbook (Higgins 2011) (16). IQ statistic values of 25%, 50% and 75% correspond to low, moderate and high levels of heterogeneity, respectively. If the IQ statistic estimate is greater than 50%, we used a random effect model to account for such heterogeneity.

Assessment of reporting biases

In line with standard Cochrane methodology guidelines, a funnel plot was not needed as our study only included 2 RCTs (Higgins 2011) (16).

Data analysis:

We analyzed our data using review manager. Depending on heterogeneity we either used fixed effect model (IQ<75%) or random effect model (IQ>75%)

Subgroup analysis and investigation of heterogeneity

Due to the limited number of studies included we were unable to carry any subgroup analysis. If more trials were available it would have been suitable to analyze according to age (more vs. less than 65 years), gender (Male vs. Female), Follow up time (more vs. less than 12 months), and generation of cryoablation used (1st vs 2nd vs

3^{rd}).

Certainty (or confidence) in the body of evidence for an outcome

We downgraded the evidence from high certainty to moderate, low or very low certainty for serious or very serious study limitations (risk of bias), indirectness and inconsistency of evidence, imprecision of effect estimates or potential publication bias using the guidance developed by the Cochrane Handbook (Higgins 2011), and the GRADE working group (Atkins 2004).

Results:

Search Results of our Search Strategy:

We compiled 9244 publications through extensive searches in online databases, grey literature, and randomized control trial registers. 7,116 studies were filtered out for not meeting the criteria of being randomized control trials, and 1,371 duplicate articles were removed. Two screeners AK and KA screened the titles and abstracts of 707 articles and excluded 697. We were left with 10 studies, 1 of which was not finished, and we were not able to get preliminary results from the authors. The screeners agreed on 2 studies but disagreed on one. A third-party screener MR arbitrated and decided that the disputed article should not be included. The articles were excluded for not being RCT's (n=2) and not exploring cryoablation or AAD's as "first-line therapy" (n=6). We were left with 2 studies that met the eligibility criteria and were included in the analysis. (**Table 1)**

The studies included in this review were conducted in Europe and America. Both randomized controlled trials were published in 2021. As for blinding they both decided to do an open blind-end point study. Both studies aimed to compare cryoballoon CA against AAD therapy in treatment naïve patients with atrial fibrillation. Of the total 303 participants in Andrade et al's (11) study, 154 patients underwent Cryoablation and 149 patients followed an AAD treatment course. In Kunis et al's (13) study, 107 participants underwent

Cryoablation and 111 participants followed an AAD treatment course out of a total of 218 randomized participants. Both studies also included a follow-up time of 12 months where participants received periodic clinic visits, and both studies had a 90-day blanking period.

Recurrence rate:

Figure 1 is a forest plot of the percent of recurrence of any atrial fibrillation, atrial tachycardia or atrial flutter after the blanking period recorded using a Holter monitor (13) or an implanted monitor (11) that patients had on them throughout the trial period. Subgroup analyses was deemed unnecessary due to low heterogeneity was and limited number of studies included.

Total number of participants with recurrence of symptoms after the blanking period was 76 out of 261 (29%) for the Cryoablation group and 134 out of 260 (50%) for the AAD group.

The metaanalysis generated a pooled RR for overall recurrence of symptoms of 0.60 for CA Versus AAD (95% CI 0.49, 0.74, $P < 0.00001$, I2=0%), using the fixed effect model, out of the two included studies (n=521)

Serious adverse events:

All serious adverse events were reported by both studies regardless of the trials authors' judgement on if the event was related to the treatment or not.

Total number of SAE was 72 events in 55 (21%) patients out of 261 patients for the Cryoablation group and 110 events in 88 patients (34%) out of 260 patients for the AAD group.

The meta-analysis generated, a pooled RR for overall SAE of 0.66 for CA Versus (95% CI 0.46, 0.95, $P = 0.03$, I2=56%) using the random effect model, out of the two included studies (n=521) (fig. 2)

The meta-analysis generated, a pooled RR for overall patients with a minimum of 1 SAE of 0.62 for CA Versus AAD (95% CI 0.47, 0.83, P=0.001, I2=0%) using the fixed effect model, out of the two included studies (n=521) (fig. 3)

No mortalities were reported in either of the studies.

Serious adverse events related to trial:

Serious adverse events related to trial were classified by the authors of each trial.

Total number of patients with SAE related to trial was 14 patients out of 261 patients for the Cryoablation group and 10 patients out of 260 patients for the AAD group.

The meta-analysis generated, a pooled RR for overall patients with a minimum of 1 SAE of 1.40 for CA Versus AAD (95% CI 0.64, 3.09, P=0.4, I2=38%) using the fixed effect model, out of the two included studies (n=521) (fig. 4)

Discussion:

Cryoablation as a primary treatment for patients with drug naïve atrial fibrillation significantly decreased risk of recurrence of symptoms by 40% compared with AAD. Furthermore, cryoablation significantly decreased the risk of severe adverse events by 34% compared to an antiarrhythmic drug based treatment, as well as significantly decreased the risk of patients developing a minimum of 1 serious adverse events by 48%.

There is no significant impact of type of treatment in relation to severe adverse events – as evidenced by CI 0.64, 3.09 including line of no effect

Trials authors concluded that cryoablation was deemed superior to AAD, significantly reducing rate of recurrences without increasing the rate of severe adverse event. They both agreed that CA could be a favorable first line approach to treat atrial fibrillation. The results of our study strengthen the conclusion

reached by both studies and clearly demonstrates that cryoablation could be a strong candidate for Anti arrhythmic drug replacement as first line treatment for atrial fibrillation.

One major limitation of this study is the limited number of studies included. This is a relatively new area of research and there is limited literature available. Nonetheless, our study shows a promising future for cryoablation as a therapy for such people newly diagnosed with atrial fibrillation that being said, our study highlights the need for further research in the area to contribute to a more conclusive argument. We urge the research community to do more clinical trials and ultimately to maximize the quality of care provided to patients with atrial fibrillation.

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Appendix:

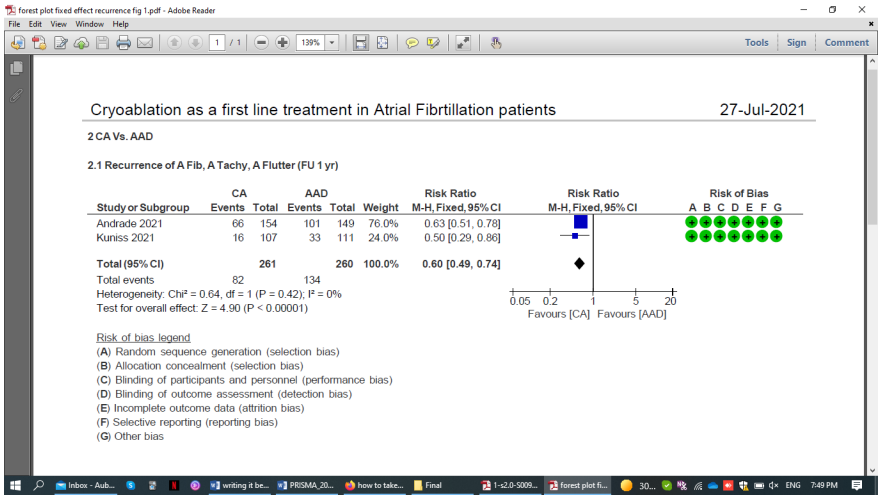

Fig. 1 Recurrence of Atrial fibrillation, Atrial tachycardia, and Atrial Flutter

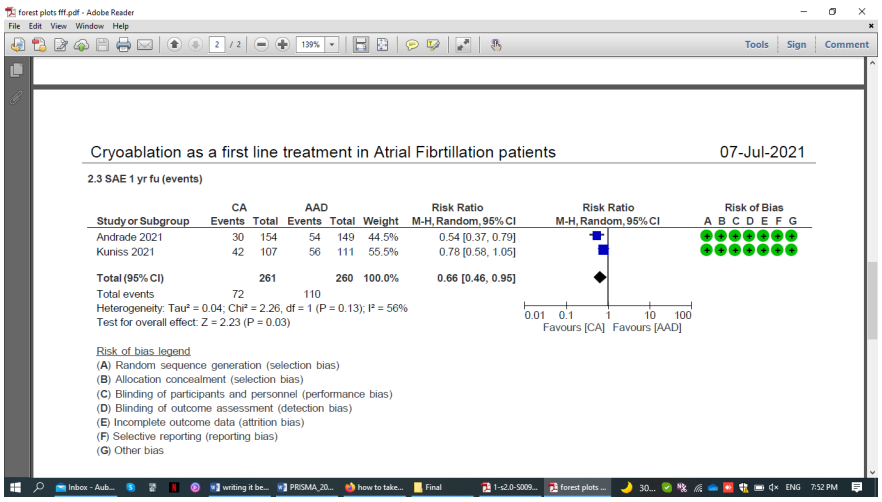

Fig. 2 Serious adverse events following CA vs. AAD

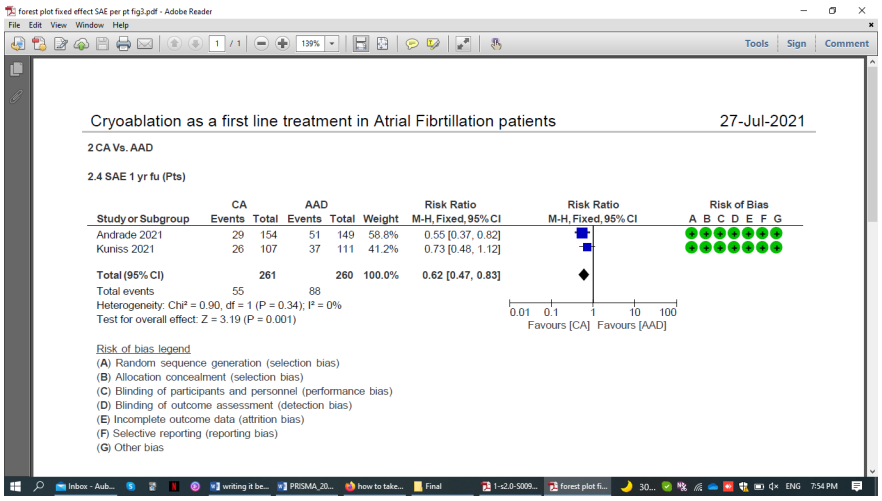

Fig. 3 number of patients with SAE post CA vs. AAD therapy

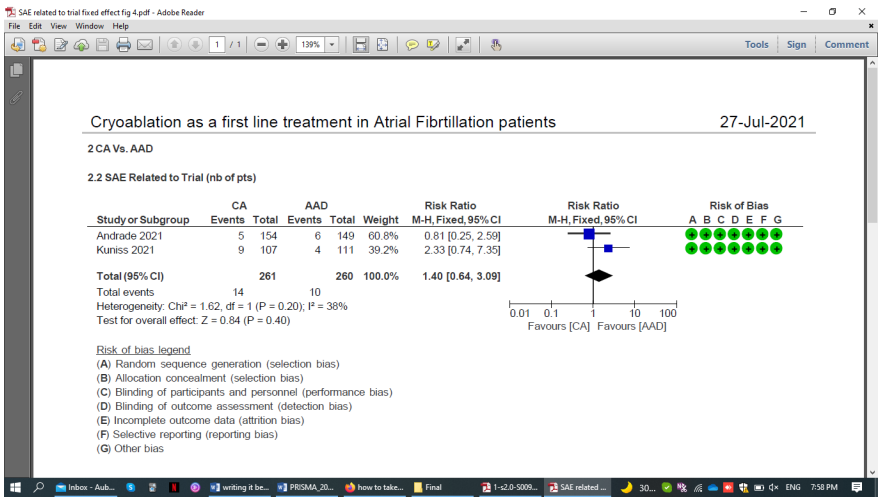

Fig. 4 patients with SAE related to therapy (CA vs. AAD

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Table 1 PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only.