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Radiofrequency Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation: Meta-Analysis of Safety and efficacy[1]

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Abstract:

Background： Radiofrequency ablation (RFA) and antiarrhythmic drugs (AAD) are the main treatments used for atrial fibrillation (AF). In recent years, a number of articles comparing the two treatments have begun to emerge. Though, the influence of follow-up time in the meta-analysis was not considered in these articles. However, more recently, large-scale clinical trial articles have included follow-up with the patients up to five years after treatment. Therefore, the aim of this study was to assess the impact of variable follow-up times on the recurrence of AF by observing both the short-term and long-term efficacy and safety of catheter ablation and antiarrhythmic drugs for the treatment of AF.

Methods and results：The primary investigators of eligible randomized controlled trials were invited to contribute standardized outcome data. Random effect summary estimates were calculated as standardized mean differences and odds ratios with 95% confidence intervals for continuous and binary outcomes. In this study, nine randomized controlled trials (n=1542 patients) were included. The rate of recurrence of AF with no limit on follow-up time, >12 months, >18 months, >24 months, >30 months, and approximately 36 months were compared.Furthermore, the gap between the RFA and AAD groups in the recurrence rate of AF was found to decrease inversely to follow-up time. When the follow-up time reached 24 months, the difference between RFA and AAD was relatively stable with an odds ratio of 0.45 (95% CI: 0.32 to 0.62). Overall, RFA decreased adverse events in the remaining trials, however AAD performed better in terms of safety and had fewer adverse events with RFA usually causing more serious complications.

Conclusion: Radiofrequency ablation is more advantageous in terms of recurrence rate of atrial fibrillation than drug therapy. In addition, the analysis suggests that this effect persists during long-term follow-up, however these benefits appear to decrease with longer follow-up time. Finally, AAD performed better in terms of safety and had fewer adverse events.

Keywords: atrial fibrillation,radiofrequency ablation, antiarrhythmic drugs, follow-up

Introduction

Atrial fibrillation (AF) is a common tachyarrhythmia affecting an estimated 33.5 million individuals globally, occurring in 1.5% of people over the age of 50[1,2]. As the age of the patient increases there are two types of treatment for AF, therapy with antiarrhythmic drugs (AADs) or radiofrequency catheter ablation (RFA). RFA is generally considered more effective AAD therapy in the treatment of recurrent symptomatic AF. However, complications with RFA, are usually more immediate and dramatic than those with AAD therapy[2-4]. With new evidence about the use of RFA in the treatment of symptomatic AF emerging, we conducted a systematic review and meta-analysis of the available data to evaluate the efficacy and safety of RFA versus AADs.

AF is the most prevalent cardiac arrhythmia causing considerable burden to patients with symptoms such as palpitations and dyspnea causing frequent emergency room visits[5,6]. Catheter ablation (CA) is the primary treatment strategy to treat AF-related patients in select populations, however repeat procedures are often needed, increasing the risk of major complications. In addition, CA is quite costly in comparison to medical therapy[7].

There are numerous clinical trial articles studying the effects of RFA and AAD treatment, over a range of different follow-up times. These include short-term follow-up studies (6–12 months[8-11]) and long-term follow-up studies (to 60 months) [12,13]. Currently there is no meta-analysis that takes into account the influence of time factors on the study results. Therefore, this meta-analysis aims to observe the effect of follow-up time on treatment outcomes.

Methods

Literature search:

A number of databases including PubMed, Google scholar and the Cochrane Library were searched for the following terms: 'Atrial fibrillation', 'Ablation', ' Radiofrequency', 'Drug', 'Antiarrhythmia', and 'Random'. All data was collected on Tuesday, March 20, 2018. Additionally, the website www.ClinicalTrials.gov was searched for ongoing trials, which have not as yet been published. Search strategies

were not limited by language or publication age.

Inclusion and exclusion criteria:

All randomized controlled trials (RCTs) comparing the efficacy and safety of RFA and AAD were collected and inclusion into the study was based on whether RFA was used as the first-line therapy or not. The patient's type of atrial fibrillation can be persistent atrial fibrillation or paroxysmal atrial fibrillation. The following exclusion criteria was applied in this study: 1) Studies reporting trials of different ablation techniques without medical management arms were not considered; 2) studies reporting RFA rate control trials were not considered; and 3) studies reporting efficacy after-ablation AAD and AAD-free trials were not included.

Data extract:

For each eligible RCT, the general research and procedural features were recorded, using the Cochrane Assessment Bias Risk Tool to Assess Risk of Bias[14]. Methodological quality of randomized controlled studies was assessed using the Cochrane risk bias assessment tool. After assessment, the included studies were designated "low risk (-)," "high risk (+)," or "unclear risk (?)." The bias of 9 documents is shown in Figure 2.

Statistical analysis:

All statistical analyses were performed using the software Review Manager version 5.3. Differences in continuous variables were reported as mean and 95% confidence interval (95% CI). Differences in dichotomous variables and outcome endpoints were reported as odds ratio or risk ratio (OR) with 95% CI.

The natural logarithm of hazard ratios and the estimated standard error of each study was entered into the software to estimate the pooled OR for freedom from recurrent arrhythmias by generic inverse variance analysis. When hazard ratios were not available, these were estimated from the survival curves of individual studies using a graphical approach. Random-effects analysis was performed; however, sensitivity analysis or meta-regression analysis was not performed because of the small number of eligible studies.

Heterogeneity was assessed using the I^2 statistic, where $I^2 < 50\%$ was considered as non-important heterogeneity. For these outcomes, the longest available follow-up data per RCT were included in the meta-analysis and $P < 0.05$ was considered statistically significant.

Results

The study selection steps are summarized in Figure 1. A total of 2341 articles were identified in the literature search. After reviewing full text of potentially suitable articles, nine articles fulfilling the selection criteria were included in this analysis[8-13,15-17].

Characteristics of the eligible studies:

The meta-analysis included eight multicenter studies and one single- center study, with a total of 1542 patients(849 in the RFA group and 693 in the AAD group). The main characteristics of these studies were showed in table 1.

Recurrence of atrial fibrillation:

In this study the rates of recurrence from nine trials were analyzed and as seen in Figure 3. 258/849 and 369/693 patients had AF recurrence after treatment with RFA and AAD respectively. Our analysis showed that RFA had a better performance in reducing recurrence of any AF in patients(P<0.01, OR 0.31, 95% CI: 0.24-0.39). Heterogeneity on the data was a little large (I^2= 60%) and After sensitivity analysis, found it might be due to the different follow-up times in each study. So we decided to analyze the impact of different follow-up times on the recurrence rate of atrial fibrillation.

In order to explore the effect of follow-up time on the outcome variable, we also analyzed the studies of the follow-up time of 12 months or more (Figure 4), 18 months or more (Figure 5), 24 months or more (Figure 6), 30 months or more (Figure 7) and 36 months or more (Figure 8) respectively. The relationship between follow-up time and the OR of the recurrence rate of AF in patients treated with RFA and AAD is seen in Figure 9. It was noted that the initial effect on the rate of reoccurrence of AF is far greater when patients are treated with RFA than when treated with AAD, but as the follow-up period continues the OR value increases, indicating that the difference in

the recurrence rate of AF between patients treated with RFA and AAD decreases. The OR stabilized at 0.45 when the follow-up time reached 24 months or more.

Death

It can be seen in Figure 10，37 patients died in the RFA group with 849 patients compared with 61 deaths in the AAD group with 693 patients. In terms of all-cause mortality, RFA also performed better. AAD group has more deaths.(OR 0.56; 95% CI: −0.36 to 0.86; I^2=0%)

Adverse events

Eight studies had adverse events data available. Shown in Figure 11, the use of AADs as a treatment for AF has increased odds in the incidence of adverse events (random-effects OR = 1.29; 95% CI:0.88 to 1.88; I^2= 16%).

Discussion

The radiofrequency ablation group did not receive any antiarrhythmic drug treatment at first, and only received targeted anticoagulant therapy. But with time goes on and the recurrence of atrial fibrillation, many patients begin to receive antiarrhythmic drugs, which may affect the long-term outcome of recurrence of atrial fibrillation in the ablation group, but these will not affect our statistics, because once ablation A group of patients had a recurrence of atrial fibrillation, and his data had been recorded in our statistical results and did not affect the overall statistical analysis. In the incidence of mortality and adverse events, the use of anti-arrhythmic drugs in the radiofrequency group may bias the results, which is unavoidable.

Recurrence of atrial fibrillation

In this study, the meta-analysis of the short- and long-term efficacy and safety of RFA versus AADs for treatment of AF highlights that the recurrence rate of AF in patients treated with RFA is significantly lower than that in patients treated with AADs[18,19]. Furthermore, other articles have derived the same conclusion that the use of RFA in the treatment of AF, shows a clear superiority over AADs in patients with AF during long-term (on average 53 months) follow-up[20]. In addition, a meta-analysis was conducted on selected eligible studies with a follow-up time of 12 months, 18 months, 24 months, 30 months, and 36 months. From this, the results showed that

with a longer follow-up time, the advantage of RFA in the recurrence rate of AF decreased. However, RFA still performed better than AAD in the studies that included a follow-up time of 36 months or more.

Mortality rate

In five studies there were 98 (6.4%) cases of death, due to a number of different of causes. It was found that the use of RFA in the treatment of AF reduced the mortality rate in patients (OR 0.56; 95% CI: −0.36 to 0.86; I = 0%). Of these five studies, the most deaths were recorded in the study conducted by Marrouche *et al*[12]. With 72.3% of all deaths noted in this analysis, found in this study. Despite there being almost no difference in current studies in the mortality rate of the patients treated with RFA or AAD, this analysis found that RFA can reduce the patient's mortality rate.

Adverse events

It was found that treatment with AADs has increased odds radio in the incidence of adverse events (random-effects OR =1.29; 95% CI: 0.88 to 1.88; I^2 = 16%). However, patients treated with RFA are often prone to serious complications. For example, among six adverse events recorded in the study conducted by Morillo *et a*[16]. In the RFA group, four patients had tamponade and one patient had severe pulmonary vein stenosis. On the other hand, there were three adverse events in the patients treated with AADs, two cases of unexplained syncope and one case of atrial flutter with a 1:1 atrioventricular conduction.

Limitations

In this study, there was some methodological heterogeneity noted between the different studies, with the ablation techniques differing slightly. This difference in technique may have an effect on the short-term and/or long-term success rate of surgery as well as the incidence of complications, and thus could have affected the results of this analysis. Similarly, AADs and anticoagulant therapy protocols are not exactly the same between trials, the selection of antiarrhythmic drugs was left to the discretion of the investigator, and dosages were based on guidelines. At the same time, in some studies, the basic situation of patients, RFCA surgery and the detection

method of AF recurrence are slightly different, which may affect the experimental results.

Conclusions

In this study, when compared to the use of AADs, RFA was found to reduce the recurrence rate of AF. This analysis also suggests that this increased protection persists during long-term follow-up, however, they tend to decrease with longer follow-up time. In terms of safety, AAD was found to have increased safety with fewer adverse events noted. Additionally, it should be noted that RFA is known to cause more serious complications.

Declaration of interests

We declare no conflict of interests in relation to this paper.

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figure legend

Figure 1.Literature Search evaluation

Figure 2. Literature quality evaluation

Figure 3. Summary Arcsine Differences (95% Confidence Intervals) of the Effects of

Figure 4. Summary Arcsine Differences (95% Confidence Intervals) of the Effects of Radiofrequency Ablation and Antiarrhythmic Drug Therapy on Recurrence of atrial fibrillation(more than 12 months follow-up time)

Figure 5. Summary Arcsine Differences (95% Confidence Intervals) of the Effects of Radiofrequency Ablation and Antiarrhythmic Drug Therapy on Recurrence of atrial fibrillation(more than 18 months follow-up time)

Figure 6. Summary Arcsine Differences (95% Confidence Intervals) of the Effects of Radiofrequency Ablation and Antiarrhythmic Drug Therapy on Recurrence of atrial fibrillation(more than 24 months follow-up time)

Figure 7. Summary Arcsine Differences (95% Confidence Intervals) of the Effects of Radiofrequency Ablation and Antiarrhythmic Drug Therapy on Recurrence of atrial fibrillation(more than 30 months follow-up time)

Figure 8. Summary Arcsine Differences (95% Confidence Intervals) of the Effects of Radiofrequency Ablation and Antiarrhythmic Drug Therapy on Recurrence of atrial fibrillation(more than 36 months follow-up time)

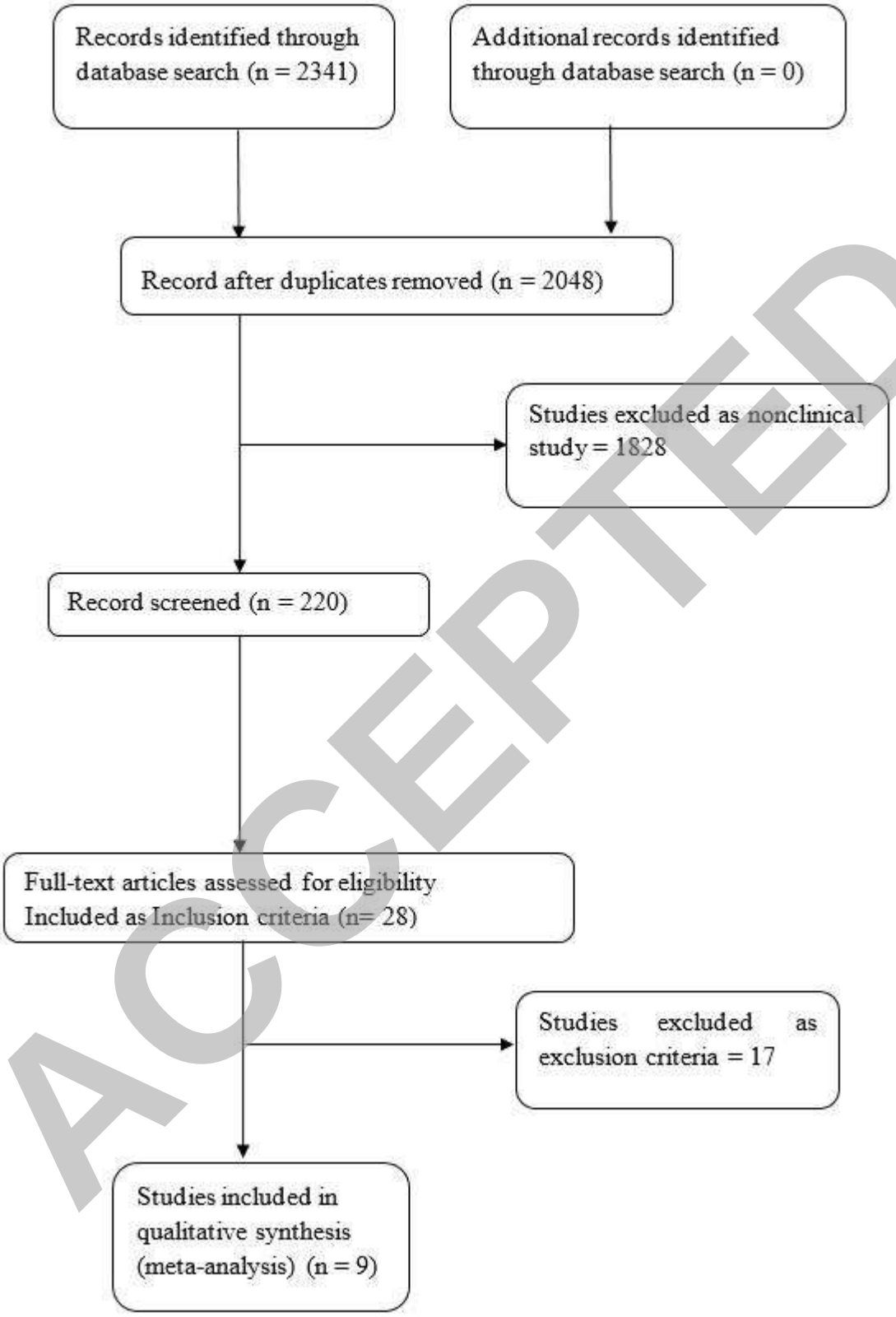
Figure 9. OR value line chart

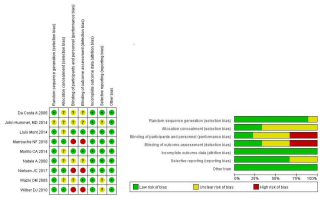
Figure 10.Summary Arcsine Differences (95% Confidence Intervals) of the Effects of Radiofrequency Ablation and Antiarrhythmic Drug Therapy on All-Cause Mortality

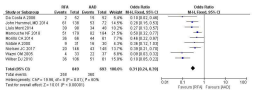
Figure 11.Summary Arcsine Differences (95% Confidence Intervals) of the Effects of Radiofrequency Ablation and Antiarrhythmic Drug Therapy on adverse events

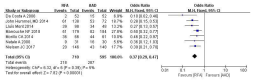
Table 1. Characteristics of randomized trials comparing the use of RFA and AADs in the treatment of AF

Author/study (Year)	Study type	Dates	Paroxysmal AF (%)	Age (years, mean)	Male (%)	Number of Patients		Max follow-Up period (months)
						RFA	AAD	
Morillo CA 2014	Multicenter	2006–2010	100	55.3	75.6	66	61	24
Natale A 2000	Multicenter	N/A	100	66.5	68.9	31	30	33
Da Costa A 2006	Multicenter	2002–2006	N/A	78.0	80.8	52	52	19
Marrouche NF 2018	Multicenter	2008–2016	32.5	64	85.7	179	184	37.8
Lluís Mont 2014	Multicenter	2009–2011	0	55.0	77.4	98	48	12
Nielsen JC 2017	Multicenter	2005–2009	100	55.0	70.0	146	148	60
John Hummel, MD 2014	Multicenter	2007–2010	0	60.0	83.3	138	72	6
Wazni OM 2005	Multicenter	2001–2002	95.7	53.5	N/A	33	37	12
Wilber DJ 2010	Multicenter	2004–2007	100	55.7	66.5	106	61	9









Study or Subgroup	RFA Events	RFA Total	AAD Events	AAD Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Da Costa A 2006	2	52	15	52	9.9%	0.10 [0.02, 0.46]
Marrouche NF 2018	51	179	82	184	39.7%	0.50 [0.32, 0.77]
Morillo CA 2014	36	66	44	61	14.3%	0.46 [0.22, 0.97]
Natale A 2000	9	31	16	30	7.9%	0.36 [0.12, 1.03]
Nielsen JC 2017	42	116	63	111	28.2%	0.43 [0.25, 0.74]
Total (95% CI)		**444**		**438**	**100.0%**	**0.42 [0.32, 0.56]**
Total events	140		220			

Heterogeneity: Chi² = 4.12, df = 4 (P = 0.39); I² = 3%

Test for overall effect: Z = 5.89 (P < 0.00001)