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Radiofrequency ablation vs. antiarrhythmic drug therapy as first line treatment of symptomatic atrial fibrillation: systematic review and meta-analysis

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Aims New evidence about first-line radiofrequency catheter ablation (RFA) in symptomatic atrial fibrillation (AF) has emerged. In a single study the comparative treatment effect is potentially diminished by the high rate of cross-over to the alternative therapy. Therefore, we conducted a systematic review and meta-analysis of the available data to further evaluate the efficacy and safety of RFA vs. antiarrhythmic drugs (AADs).

Methods and results Five databases were searched for randomized controlled trials comparing RFA and AAD therapy as first-line treatment of AF in August 2014. Three studies with 491 patients with recurrent symptomatic AF were included. The patients were relatively young and the majority of them had paroxysmal AF (98.7%) and no major comorbidity. Radiofrequency catheter ablation was associated with significantly higher freedom from AF recurrence compared with AAD therapy [risk ratio (RR) 0.63, 95% confidence interval (CI) 0.44–0.92, $P = 0.02$]. The difference in the rate of symptomatic AF recurrences was not statistically significant (RR 0.57, 95% CI 0.30–1.08, $P = 0.09$). There was one procedure-related death and seven tamponades with RFA, whereas symptomatic bradycardia was more frequent with AAD therapy.

Conclusion Radiofrequency catheter ablation seems to be more effective than medical therapy as first-line treatment of paroxysmal AF in relatively young and otherwise healthy patients, but may also cause more severe adverse effects. These findings support the use of RFA as first-line therapy in selected patients, who understand the benefits and risks of the procedure.

Keywords Atrial fibrillation • Catheter ablation • Antiarrhythmic drug • Outcome • Meta-analysis • Systematic review • First-line treatment

Introduction

Radiofrequency catheter ablation (RFA) is generally considered more effective than antiarrhythmic drug (AAD) therapy in the treatment of recurrent symptomatic atrial fibrillation (AF). However, RFA has mostly been studied in the setting of initially failed AAD therapy and the follow-up in these studies has been only 12–14 months.[1–4] The concept '*first* do no harm' plays a key role in management of AF.[5,6] It is well established that both RFA and AAD therapy carry a risk of severe complications and concerns about their safety have repeatedly been raised.[5–11] Previous meta-analyses suggest that RFA causes fewer but more severe complications than AAD therapy.[1,2,4] Complications with RFA, as well as with any invasive cardiac intervention, are usually more immediate and dramatic than those with medical therapy.[1,2,4]

Although controversy still exists, several findings justify implementation of RFA as a first-line treatment for selected patients with paroxysmal AF.[12–14] In particular, because AF begets AF[15] it is likely that early ablation may be more efficient and delay or prevent progression of the disease compared with its later application. Recently new long-term data comparing RFA and AAD therapy as first-line treatment of symptomatic AF has emerged.[16,17] In these studies, long-term Holter monitoring or frequent transtelephonic electrocardiogram (ECG) transmissions were used to collect data not only on symptomatic

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but also on asymptomatic AF recurrences. Unfortunately, however, like in the previous studies many patients in the AAD group underwent RFA after the initial medication had failed. The present meta-analysis aims to diminish the impact of cross-over and other confounding factors and to provide further information on the safety and efficacy of RFA as first-line therapy for symptomatic AF.

Methods

Literature search and data extraction

We searched PubMed, Scopus, and Cochrane Library on 13 August 2014, as well as reference lists of retrieved articles. The search strategy was not restricted by language or year of publication. We used the following search terms: 'atrial fibrillation', 'ablation', 'isolation', 'drug*', 'antiarrhythmic', 'medica*', and 'random*'. Unpublished studies or grey literature were sought from clinicaltrials.gov and Google.

Studies meeting both of the following criteria were included: (i) prospective randomized clinical trial evaluating RFA vs. AAD therapy as first-line treatment of symptomatic AF; (ii) Availability of data on freedom from recurrent symptomatic or asymptomatic AF episodes as well as proportion of patients with recurrent symptomatic AF.

Two reviewers (A.H. and P.R.) screened the titles and available abstracts from the literature search results and identified studies for assessment of the full text. Disagreements were solved by a third reviewer (F.B.) for resolution. Information extracted onto pre-specified data forms included study characteristics (authors, year of publication, study period, study design, sample size), the population (mean age, left atrial size, prevalence of paroxysmal AF, $CHADS_2$ score, and prior use of beta blockers), risk of bias (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other possible biases), exposure (methods of assessment and its timing) and outcome measures (recurrence of symptomatic and asymptomatic AF as well as any adverse event associated with treatment methods). Relevant unreported data were retrieved from all available sources and authors were contacted if necessary.

Study outcomes

The primary outcome endpoints of this analysis were freedom from recurrent symptomatic or asymptomatic AF episodes as well as proportion of patients without recurrent symptomatic AF. If the occurrence of atrial tachycardia or atrial flutter in addition to AF was considered as a main outcome endpoint (RAAFT-2 study), these were included in the analysis.

Secondary outcome endpoints were proportion of cross-over to the alternative therapy, additional ablation after the initial therapy with either RFA or AADs had failed, cardiac tamponade, pulmonary vein (PV) stenosis >70%, symptomatic bradycardia, stroke, atrial flutter with 1:1 atrioventricular conduction, syncope, and hospitalization.

Statistical analysis

Statistical analysis was performed using Review Manager 5.3 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).[18] 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 (RR) with 95% CI. The natural logarithm of hazard ratios and the estimated standard error of each study were entered in to Review Manager to estimate pooled RR 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 by using a graphical approach that shows time trends.[19] Heterogeneity was assessed by using I^2 statistic. $I^2 < 40\%$ was considered as non-important heterogeneity. We performed only random-effects analysis. Sensitivity analysis or meta-regression analysis was not performed because of the small number of eligible studies. $P < 0.05$ was considered statistically significant.

Results

A total of 1238 articles were identified in the literature search. The study selection is summarized in *Figure 1*. After reviewing full text of potentially suitable papers, three articles[16,17,20] fulfilling the pre-specified selection criteria were included in this analysis.

Characteristics of the eligible trials

This meta-analysis included three prospective randomized multicentre trials designed to compare the efficacy (i.e. recurrence of AF after the initial therapy) and safety of RFA vs. AAD therapy as first-line strategy for treatment of symptomatic AF.[16,17,20] The main characteristics of these studies are summarized in *Table 1*. A total of 491 patients were randomized and 488 of them (244 in the RFA a group and 244 in the AAD group) were available for the analysis. The main inclusion criterion was symptomatic AF without previous treatment with class I or class III AADs. Exclusion criteria are reported in details in *Table 1*.

The risk of bias in the individual studies is summarized in *Table 2*. Blinding of participants and study personnel was not feasible and blinding of outcome assessment was reported in two studies (RAAFT-2, MANTRA-PAF) (*Table 2*). Based on these characteristics, the RAAFT-2 and MANTRA-PAF trials were considered at low risk of bias as the domains of unclear risk of bias (allocation concealment) were unlikely to have seriously altered the results of the main outcome endpoint. The RAAFT-1 trial was possibly biased due to unblinded outcome assessment. The AAD treatment was chosen by the investigator. In all three studies the most commonly used AADs were flecainide, propafenone, and sotalol. The use of amiodarone was allowed in two studies (RAAFT-2, MANTRA-PAF) and the use of dofetilide in one study (RAAFT-2). In the RFA group supplementary AAD therapy was allowed during the three months blanking period after the procedure in two studies (RAAFT-2, MANTRA-PAF) (*Table 3*). Follow-up was 1 year in the RAAFT-1 study and 2 years in the other studies. The primary and secondary outcome endpoints are listed in *Table 3*.

Baseline characteristics

There were no significant differences in the baseline characteristics of the randomized patients (*Table 4*). In particular, the mean diameter of the left atrium ($P = 0.24$), the rate of paroxysmal AF (243/245 vs.

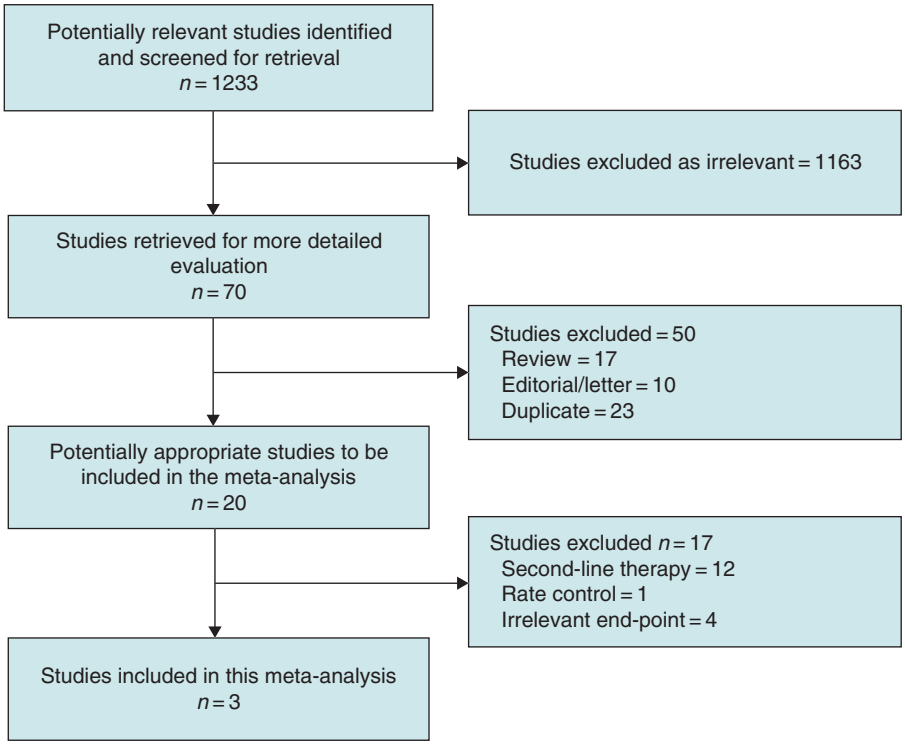

Figure 1 Study selection for systematic review of radiofrequency ablation or antiarrhythmic drug treatment as first-line treatment of atrial fibrillation.

242/246 patients, $P = 0.43$), use of beta-blockers (165/245 vs. 166/246 patients, $P = 0.99$) did not differ between the study groups. Data on $CHADS_2$ were available in two studies (RAAFT-2, MANTRA-PAF). The score did not differ between the study groups ($P = 0.43$).

Primary clinical outcome

The timeline of recurrent symptomatic or asymptomatic AF detected by Holter or event monitoring was evaluated in all three studies (*Table 3*). MANTRA-PAF and RAAFT-2 investigators reported the specific hazard ratios, whereas in the RAAFT-1 it was estimated using Tierney's method.[19] Our analysis showed that RFA was associated with significantly higher freedom from recurrent AF ($P = 0.02$, RR 0.63, 95% CI 0.44–0.92, I^2 38%) (*Figure 2*). The RAAFT-1 trial was possibly biased by lack of blinding of outcome assessment. When it was excluded from the analysis, RFA was still associated with significantly higher freedom from recurrent AF ($P = 0.03$, RR 0.70, 95% CI 0.51–0.96, I^2 28%). In the RAAFT-2 study not only AF but also the occurrence of atrial tachycardia and flutter was considered as a main outcome endpoint. When RAAFT-2 data were excluded from the analysis, the difference between the treatment groups was not statistically significant ($P = 0.19$, RR 0.60, 95% CI 0.28–1.29, I^2 57%).

Many patients had no symptoms during the AF or other supraventricular tachyarrhythmia episodes detected by the Holter or event monitoring. When the asymptomatic patients were excluded the absolute number of patients with recurrent symptomatic AF was higher in the AAD than in the RFA group (102 vs. 66 patients) but the difference was not statistically significant ($P = 0.09$, RR 0.57, 95% CI 0.30, 1.08, I^2 74%) (*Figure 3*).

Secondary clinical outcomes

The secondary clinical outcome events and effects estimate in patients who underwent RFA or AAD treatment for symptomatic AF in the eligible randomized studies are summarized in *Table 5*. In the RAAFT-1 trial data on cross-over were reported only after the pre-specified study period. By assuming that in the RAAFT-1 trial no cross-overs occurred during study period, cross-over was significantly more frequent in the AAD than in the RFA group (19/238 vs. 80/242, $P < 0.0001$, RR 0.24, 95% CI 0.15–0.38, I^2 0%). The rate of additional RFA therapy after randomization did not differ between the study groups (78/238 vs. 80/242 patients, $P = 0.59$, RR 0.68, 95% CI 0.16–2.81, I^2 94%). Data on pericardial tamponade were available from two studies (RAAFT-2, MANTRA-PAF). There were four tamponades in the RFA group in the RAAFT-2 and three in the MANTRA-PAF trial, respectively. Hence, as expected the risk of this complication was higher among patients treated with RFA than with AADs (7/212 vs. 0/209 patients, $P = 0.05$, RR 7.83, 95% CI 0.99–62.09, I^2 0%). Symptomatic bradycardia was less frequent with RFA than with AADs (0/172 vs. 8/181 patients, $P = 0.04$, RR 0.12, 95% CI 0.02–0.95, I^2 0%). No significant difference was observed in terms of other outcome endpoints (*Table 5*). Severe PV stenosis was observed in one patient after ablation ($P = 0.53$).

Table 1 Characteristics of randomized trials comparing first-line radiofrequency ablation vs. antiarrhythmic drugs for atrial fibrillation

Study	First author	Year	Study period	Type of study	No. of randomized patients (RFA/drugs)	No. lost to follow-up (RFA/drugs)	No. of patients included in the in primary analysis (RFA/drugs)	Inclusion criteria	Exclusion criteria
RAAFT-1	Wazni	2005	2001–2002	Prospective, randomized, multicentre	33/37	1/2	32/35	Symptomatic AF for at least 3 months not treated by AADs	Age <18 years or >75 years, previous AF ablation, previous cardiac surgery, previous treatment with AADs, contraindication to OAC treatment
MANTRA-PAF	Cosedis-Nielsen	2012	2005–2009	Prospective, randomized, multicentre	146/148	0/0	146/148	Symptomatic PAF for at least 6 months. No episodes >7 days. No previous or ongoing treatment with class IC or III AADs	Age >70 years, previous or ongoing class IC or class III AADs, contraindication to class IC or class III AADs, previous ablation, LA diameter >5.0 cm, LVEF <40%, contraindication to OAC, moderate-to-severe mitral valve disease, NYHA III-IV, expected surgery for structural heart disease, secondary atrial fibrillation
RAAFT-2	Morillo	2014	2006–2010	Prospective, randomized, multicentre	66/61	0/0	66/61	Symptomatic PAF for at least 6 months not treated by AADs	Age <18 years or >75 years, previous treatment with AADs, LVEF <40%, LA diameter >5.5 cm, left ventricular wall thickness >1.5 cm, valve disease, coronary artery disease, previous cardiac surgery within 6 months, previous AF ablation

AAD, antiarrhythmic drug; RFA, radiofrequency ablation; AF, atrial fibrillation; PAF, paroxysmal atrial fibrillation; OAC, oral anticoagulation; LVEF, left ventricular ejection fraction; LA, left atrial.

Table 2 Risk of bias in randomized trials comparing first-line radiofrequency ablation vs. antiarrhythmic drug therapy for symptomatic atrial fibrillation

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
RAAFT-1	Low risk of bias	Unclear risk of bias	High risk of bias	High risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
RAAFT-2	Low risk of bias	Unclear risk of bias	High risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
MANTRA-PAF	Low risk of bias	Unclear risk of bias	High risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias

Discussion

The results of our meta-analysis show that the long-term risk of recurrent AF is significantly lower among patients treated with RFA than with AADs. Compared with the general AF population the patients in this analysis were much younger and otherwise healthier. Majority of them had paroxysmal AF and minimal-to-no cardiovascular disease. Therefore, extreme caution is needed when extrapolating these data to other patients groups.

Only prospective, randomized multicentre trials with rather uniform design and patient population were included in our meta-analysis. Although blinding of participants and study personnel was not feasible, the risk of methodological bias was considered low. However, several differences need to be considered. For example, in the MANTRA-PAF trial, the primary endpoint was AF burden, whereas time to first AF recurrence was a secondary (although predefined) endpoint. Although long-term ECG monitoring was used in all studies, there was some heterogeneity in the follow-up methods and adherence to AF monitoring. Episodes lasting $\geq$15, $\geq$30, and $\geq$60 s were recorded in RAAFT-1, RAAFT-2, and MANTRA-PAF, respectively. Nevertheless, this had probably no effect on the proportional efficacy between the study groups. There were also slight differences in the RFA techniques and AAD therapy. Additional lesions besides PV isolation were allowed in RAAFT-2 and MANTRA-PAF study and in the MANTRA-PAF trial electrical isolation of the PVs was not confirmed by circular mapping catheter in all patients. Moreover, the use of irrigated and non-irrigated ablation catheters varied.

Efficacy and safety of radiofrequency catheter ablation

In patients with drug-refractory paroxysmal AF, the results of multiple clinical trials have demonstrated the superiority of catheter ablation over AAD therapy in long-term maintenance of sinus rhythm. In addition, RFA improves quality of life.[7,21,22] Our data are in agreement with these findings and provide further support to the current guideline recommendation that RFA can be used as an initial treatment strategy in selected patients with paroxysmal AF. About one-third of the patients initially in or crossing over to ablation therapy required reablation, which is in line with the results of previous reports.[22]

Radiofrequency catheter ablation therapy carries a risk of severe complications and concerns about its safety has repeatedly been raised.[9,10] Data on the safety of RFA have been widely reported from high volume centres, international surveys, and previous meta-analyses.[1,2,4,9,10,23–26] Radiofrequency catheter ablation-related complications usually are more immediate and dramatic than those with medical therapy.[1,2,4] In our analysis, there was one death after a stroke related to the RFA procedure. The most prominent complication was cardiac tamponade that occurred in seven patients (1.7%). PV stenosis was rare (0.2%). Asymptomatic PV stenosis was searched by routine computed tomograhy or magnetic resonance imaging scans 3 months after ablation on RAAFT-1 and RAAFT-2 but not in the MANTRA-PAF trial. Taken together, current and previous data indicate that RFA causes more severe adverse effects than AAD therapy. This underlines the importance of patient selection and operator experience.[6,9,10,22]

Efficacy and safety of antiarrhythmic drug therapy

According to the previous data, the efficacy of currently available AADs in treatment of AF is poor and AF relapses are common.[1–4,6,8] In contrast, the overall efficacy of early AAD treatment in our meta-analysis appeared to be rather good, although cross-over due to inefficacy was significantly more common among patients treated with AADs (33%) than RFA (8%). The patients in the current meta-analysis were younger, had lower comorbidity and shorter history of AF than those in the AFFIRM study, which showed no benefit from rhythm control compared with rate control.[7] Hence, a prompt intervention with either ablation or AADs plays a key role in management of AF.

Supplementary antiarrhythmic medication is commonly used during the blanking period after AF ablation. It has been shown to reduce AF relapses and give time for the ablation lesions to consolidate.[22,27–29] Antiarrhythmic drug therapy was allowed during the first 3 months after in ablation in the MANTRA-PAF and RAAFT-2 trial, but no blanking period was used in the RAAFT-1 study. After the blanking period adjuvant AAD therapy has been used to suppress symptoms in patients with partial response to ablation.[10] In the MANTRA-PAF trial, 8% of the patients in the RFA group were using AADs at 2 years follow-up.[16]

Table 3 Methods and outcome endpoints in the randomized trials comparing first-line radiofrequency ablation vs. antiarrhythmic drugs for atrial fibrillation

Study	Ablation method	Anticoagulation after AF ablation	AAD therapy after AF ablation	AAD therapy	Anticoagulation with antiarrhythmic drug treatment	Follow-up period	Primary endpoint	Secondary endpoints
RAAFT-1	RFA with an 8 mm catheter (Biosense Webster). Electrical disconnection of all four pulmonary vein antra from the left atrium	Warfarin with a target INR 2-3 for at least 3 months. Warfarin was continued in case of recurrent AF or >50% narrowing of a pulmonary vein was detected at CT 3 months after procedure	Beta-blocker therapy according to the physician preference	Flecainide, propafenone, sotalol and beta-blocker therapy according to physician preference	Warfarin with a target INR 2–3 throughout the study	1 year	Recurrence of symptomatic or asymptomatic AF >15 s during Holter or event monitoring	Hospitalization, quality of life (SF-36)
RAAFT-2	RFA with confirmation of entrance block into each pulmonary vein. Additional ablation lesions were allowed. Selection of instruments and navigation system was left to the discretion of the investigator	Warfarin with a target INR 2–3 for at least 3 months	AADs were allowed only during the 90-day blanking period	Propafenone, flecainide, sotalol, dofetilide, amiodarone. The selection of antiarrhythmic drug was left to the discretion of the investigator	Not stated	2 years	Recurrence of symptomatic or asymptomatic AF, atrial flutter or atrial tachycardia >30 s on ECG or transtelephonic monitor	First documented recurrence and repeated episodes of symptomatic or asymptomatic AF, atrial flutter or atrial tachycardia, quality of life (EQ-5D)
MANTRA-PAF	RFA of the pulmonary veins with a 3.5 mm irrigated tip catheter or a 8.0 mm solid tip catheter (Biosense Webster, Calif. USA) with elimination of all high-frequency electrical activity with an amplitude > 0.2 mV inside the encircled areas. Additional ablations outside the pulmonary veins were allowed	Warfarin with a target INR 2–3 for the whole study period was recommended	AADs were allowed during the initial 3 months after ablation	Flecainide, propafenone, amiodarone, sotalol	Warfarin with a target INR 2–3 for the whole study period was recommended	2 years	Percentage of time in AF on each and on all Holter recordings	Freedom from any AF, freedom from symptomatic AF, cumulative and per-visit burden of symptomatic AF, time to first recurrence of AF after the blanking period, atrial flutter longer than 1 min, quality of life (SF-36)

RFA, percutaneous radiofrequency catheter ablation; AAD, antiarrhythmic drug; AF, atrial fibrillation; RFA, radiofrequency ablation; CT, computed tomography.

Table 4 Analysis of baseline characteristics between patients who underwent radiofrequency ablation or antiarrhythmic drug treatment for atrial fibrillation in three randomized studies

Baseline variables	No. of studies	Participants	*P* value	Effect estimate OR or MD (95% CI)	I^2
Age	3	491	0.10	1.40 (−0.27, 3.08)	0%
Left atrial size	3	491	0.24	−0.13 (−0.35, 0.09)	73%
Paroxysmal AF	3	491	0.43	2.01 (0.36, 11.25)	0%
CHADS2 <2	2	421	0.43	1.28 (0.69, 2.36)	0%
Beta-blockers	3	491	0.99	1.00 (0.68, 1.46)	0%

AF, atrial fibrillation; MD, mean difference; OR, odds ratio; CI, confidence interval.

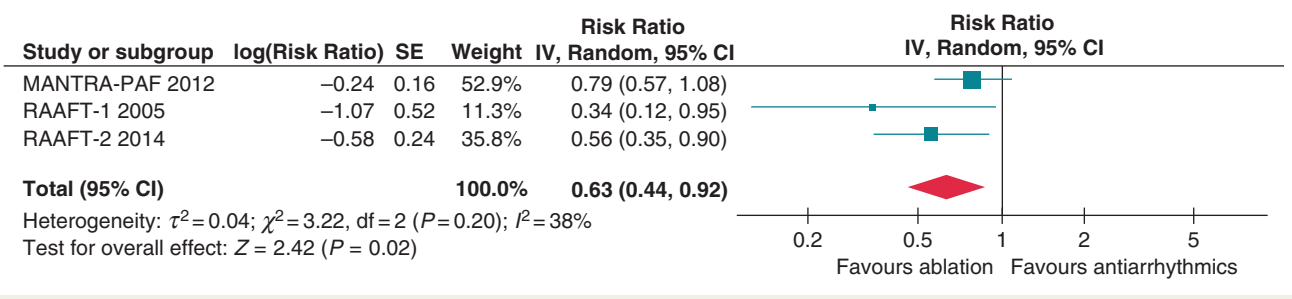

Figure 2 Forest plot showing the risk of recurrence of atrial fibrillation after radiofrequency ablation or antiarrhythmic drug treatment in three randomized studies. RAAFT-2 study included also the occurrence of atrial tachycardia and flutter.

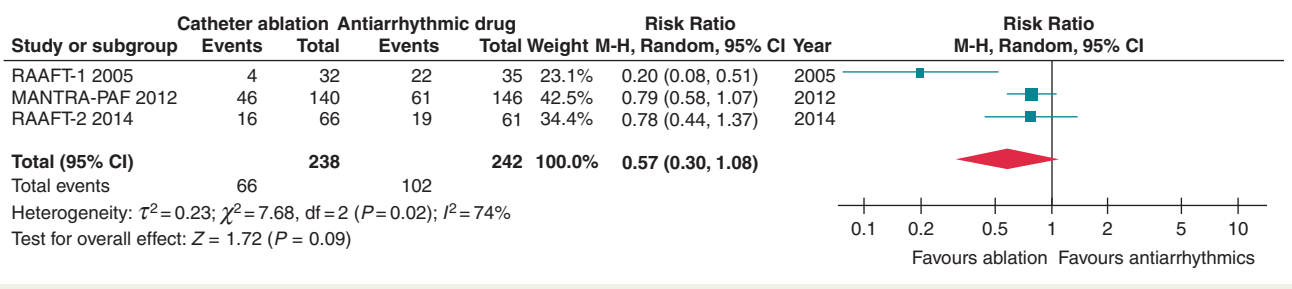

Figure 3 Forest plot showing the risk of symptomatic atrial fibrillation after radiofrequency ablation or antiarrhythmic drug treatment in three randomized studies.

In our analysis, there was one death related to RFA and no deaths related to AAD therapy. In keeping with this, the studies by Andersen *et al.*[30] and Kirchhof *et al.*[31] showed no excess mortality with medium term use of AADs. However, the data on long-term safety and efficacy of AADs are scant. During long-term AAD therapy, serious adverse events and mortality are mostly related to structural heart disease or to permanent AF.[32–34] and may occur late upon development of cardiac diseases. Recently the AFFIRM investigators reported that the risk of mortality and cardiovascular hospitalizations was significantly lower during a 5 years follow-up in the rate-control arm compared with the AAD arm.[35] Hence, long-term AAD use requires repeated evaluation and careful follow-up of the patients for late complications.

The majority of the patients in the studies included in the current meta-analysis were treated with class IC AADs. All patients underwent throughout cardiovascular examinations to exclude structural heart diseases before randomization. Therefore, our results are not directly applicable to AF patients with severe structural heart disease or when using other AADs.

Limitations

Our analysis has several limitations. As discussed above, although only randomized controlled trials were included in this meta-analysis,

Table 5 Outcome of patients who underwent radiofrequency ablation or antiarrhythmic drug treatment for atrial fibrillation in three randomized studies

Outcome endpoints	No. of studies	Participants	RFA 238 patients	AAD 242 patients	*P* value	Effect estimate RR (95% CI)	I^2
Symptomatic AF recurrence	3	480	66	102	0.09	0.57 (0.30, 1.08)	74%
Freedom from recurrent AF	3	480	–	–	0.02	0.63 (0.44, 0.92)	38%
Cross-over	3	480	19	80	<0.0001	0.24 (0.15, 0.38)	0%
Additional ablations	3	480	78	80	0.59	0.68 (0.16, 2.81)	94%
Tamponade	2	413	7	0	0.05	7.83 (0.99, 62.09)	0%
Pulmonary vein stenosis >70%	3	480	1	0	0.53	2.78 (0.12, 66.88)	–
Symptomatic bradycardia	2	353	0	8	0.04	0.12 (0.02, 0.95)	0%
Stroke	3	480	1	0	0.48	3.13 (0.13, 76.14)	–
Atrial flutter with 1:1 AV conduction	2	413	0	3	0.22	0.25 (0.03, 2.25)	0%
Syncope	2	413	0	3	0.21	0.25 (0.03, 2.23)	0%
Hospitalization	2	353	89	99	0.92	0.98 (0.64, 1.50)	87%

AF, atrial fibrillation; RFA, radiofrequency catheter ablation; AAD, antiarrhythmic drug therapy; RR, risk ratio; CI, confidence interval.

there was some methodological heterogeneity between the studies, especially with respect to arrhythmia detection during follow-up. It is possible that allowance of amiodarone use during the blanking period may have reduced early AF recurrences in the RFA group. However, only few patients received amiodarone during the blanking period in the eligible studies. The maximum follow-up was two years. Whether the benefit of first-line RFA is maintained at longer follow-up is not clear and warrants further investigation. The completion of MANTRA-PAF 5 years follow-up is expected to provide important information on this issue in near future.

Conclusions

Our meta-analysis suggests that RFA is more effective than AAD therapy as first-line treatment of paroxysmal AF in relatively young and otherwise healthy patients. On the other hand, RFA often causes severe adverse effects. Therefore, before offering RFA as an initial treatment the risks and benefits of the therapeutic options should be considered and explained to the patient. No recommendations on the selection of first-line treatment strategy in patients with non-paroxysmal AF and/or severe co-morbidity can be made on the basis of the current analysis.

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