REVIEW ARTICLE

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Ablation therapies for paroxysmal atrial fibrillation: A systematic review and patient-level network meta-analysis

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ABSTRACT

Introduction: Despite promising trials, catheter ablation is still regarded as an adjunct to antiarrhythmic drugs (AADs) in the treatment of paroxysmal atrial fibrillation (PAF). This study aimed to compare the effectiveness of various ablation therapies and AADs.

Method: Randomised controlled trials or propensity score-matched studies comparing atrial tachyarrhythmia recurrence among any combination of ablation modalities or AAD were retrieved. Kaplan-Meier curves and risk tables for this outcome were graphically reconstructed to extract patient-level data. Frequentist network meta-analysis (NMA) using derived hazard ratios (HRs), as well as 2 restricted mean survival time (RMST) NMAs, were conducted. Treatment strategies were ranked using P-scores.

Results: Across 24 studies comparing 6 ablation therapies (5,132 patients), Frequentist NMA-derived HRs of atrial fibrillation recurrence compared to AAD were 0.35 (95% confidence interval [CI]=0.25–0.48) for cryoballoon ablation (CBA), 0.34 (95% CI=0.25–0.47) for radiofrequency ablation (RFA), 0.14 (95% CI=0.07–0.30) for combined CBA and RFA, 0.20 (95% CI=0.10–0.41) for hot-balloon ablation, 0.43 (95% CI=0.15–1.26) for laser-balloon ablation (LBA), and 0.33 (95% CI=0.18–0.62) for pulmonary vein ablation catheter. RMST-based NMAs similarly showed significant benefit of all ablation therapies over AAD. The combination of CBA + RFA showed promising long-term superiority over CBA and RFA, while LBA showed favourable short-term efficacy.

Conclusion: The advantage of ablation therapies over AAD in preventing atrial tachyarrhythmia recurrence suggests that ablation should be considered as the first-line treatment for PAF in patients fit for the procedure. The promising nature of several specific therapies warrants further trials to elicit their long-term efficacy and perform a cost-benefit analysis.

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Keywords: Atrial fibrillation, catheter ablation, network meta-analysis

INTRODUCTION

Atrial fibrillation (AF) is a pertinent health condition that is seeing a sustained rise in global incidence and prevalence.[1] In particular, paroxysmal AF (PAF), despite its transient nature, is associated with a slow but steady progression to persistent AF[2] and increased mortality compared to patients without AF.[3] Furthermore, patients with PAF have a similar rate of ischaemic stroke as patients with persistent AF; it is thus important to address PAF to prevent future cardiovascular mortality and morbidity.[4]

Medical therapy with antiarrhythmic drugs (AADs) has long been the mainstay of PAF therapy.[5] Catheter ablation is an alternative upfront treatment with a class IIa recommendation[5] and can also be performed if AAD therapy fails; the class I recommendation only applies to patients with heart failure with reduced ejection fraction.[6] The commonly used ablation techniques in practice are radiofrequency ablation (RFA)[7] and cryoballoon ablation (CBA); others include laser balloon ablation (LBA), hot balloon ablation (HBA), and pulmonary vein ablation catheter (PVAC). Recent trials

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CLINICAL IMPACT

What is New

- In this systematic review and network meta-analysis using patient-level data from high-quality studies, catheter ablation was found to be consistently superior to antiarrhythmic drugs (AADs) for the treatment of paroxysmal atrial fibrillation (PAF) in terms of preventing atrial fibrillation recurrence.
- This finding was observed across 3 different network meta-analysis models.

Clinical Implications

- This study further cements evidence for catheter ablation as a promising alternative to AADs as the first-line treatment for PAF in patients fit for the procedure.
- Promising results of combined cryoballoon plus radiofrequency ablation in the long term, and laser-balloon ablation in the short term, highlight the need for more trials and cost-benefit analyses with long-term follow-up.

have shown significant benefit for catheter ablation as a first-line therapy for PAF, and meta-analyses have indeed advocated for ablation to replace AADs in treating PAF.[8,9] However, they were limited by low numbers of included trials, or grouping all ablation modalities as a single arm. Similarly, there are meta-analyses comparing CBA and RFA, but included studies do not usually involve an AAD arm for reference.[10,11]

Given the diversity of modalities and fragmented nature of research into the field of ablation therapies for PAF, an all-encompassing synthesis of the subject using evidence from high-quality trials is sorely needed. This can be addressed by a network meta-analysis (NMA), which is an effective method to pool effect sizes across multiple studies and modalities.[12] As randomised controlled trials (RCTs) in this field are limited in number, propensity-score matched studies (PSMs) were also the sought for pooling of individual patient data (IPD). PSMs have been shown to be empirically equivalent to RCTs in generating unbiased estimates of the efficacy of treatment, while eliminating confounding factors and biases to a large extent.[13]

Hence, the aim of this IPD-NMA was to evaluate the effectiveness of various ablation therapies or medical therapy in PAF patients from RCTs or PSMs, with atrial tachyarrhythmia recurrence as the primary outcome.

METHOD

Literature search

This systematic review and IPD-NMA were performed in line with the PRISMA Guidelines for IPD Systematic Reviews. The study design and review protocol were registered with PROSPERO (CRD42022313230).

An electronic literature search from inception to 29 October 2021 was performed on PubMed, EMBASE, Web of Science and the Cochrane Controlled Register of Trials (CENTRAL), without language restrictions. The search strategy included the concepts of PAF and various ablation modalities (Supplementary Table S1 in the online version of this article). Bibliographies of included studies were screened to ensure the inclusion of all relevant studies. The abstract and full-text review were conducted by 2 independent investigators; conflicts were resolved after discussion among all the authors in this paper.

The inclusion criteria were: RCTs or PSMs comparing any combination of ablation modalities or comparing ablation modalities against AADs in patients with paroxysmal atrial fibrillation; and provision of Kaplan-Meier curves with risk tables for atrial tachyarrhythmia recurrence (or complete study follow-up if risk tables were absent). If multiple publications of the same study were retrieved, the most recent and informative publication was included. Studies comparing ablation versus AAD without specifying the exact ablation modality were excluded, as were case reports, case series, reviews and conference abstracts.

Data extraction from included studies was conducted by 2 independent investigators using a standardised data collection template with predefined data fields including study design, patient demographics and outcomes. RCTs were assessed for risk of bias using the Cochrane Risk of Bias (RoB 2) tool for RCTs, and PSMs were assessed using the Newcastle-Ottawa Scale.

Extraction of individual patient data

Given the rapid advancements in ablation therapies in recent years, more precise methods are needed to quantify comparisons among different modalities. Hence, a graphical reconstructive algorithm[14] grounded in analysis outlined by Guyot et al.[15] was employed to attain IPD for survival from atrial tachyarrhythmia recurrence, using Kaplan-Meier curves from included studies. An IPD meta-analysis is recognised as the gold standard approach for evidence synthesis.[16,17]

Network meta-analysis

First, a Frequentist NMA was conducted to compare the treatments of CBA, RFA, CBA + RFA, PVAC, LBA, HBA and AAD. Hazard ratio (HR) estimates and their 95% confidence intervals (95% CI) for each IPD study were pooled together in a 2-stage NMA. Treatment strategies were ranked using P-scores, with higher P-scores corresponding to greater efficacy.

As Cox-based models were used to derive HRs for the aforementioned analysis, the proportional hazards assumption was verified. If the assumption was violated, restricted mean survival time (RMST) for each treatment was also analysed[18-20] using 2 measures—RMST mean difference (RMST-D) and RMST ratio (RMST-R)—which were pooled under respective Frequentist NMAs. As RMST does not utilise HRs and is applicable to nonlinear covariate relationships, it acts as a further sensitivity analysis of the first NMA. Heterogeneity was assessed via the I^2 statistic, and considered low, moderate, or considerable for I^2 values <40%, 40–75%, and >75%, respectively.[21] Cochran's Q was also used to assess for heterogeneity and inconsistency.

Due to the inclusion of non-randomised studies in the form of PSM in this study, sensitivity analysis was also performed, involving a Frequentist NMA with data from RCTs only.

A further NMA was also conducted by pooling ablation procedural times in studies that compared 2 or more ablation procedures. Outcomes were assessed as mean differences (MD), with RFA as a base comparator.

All analyses were conducted in R version 4.1.2, with $P<0.05$ regarded as indicating statistical significance. Full details of the statistical analyses are provided in the online Supplementary Methods. Ethics approval was not required as this study makes use of publicly available data.

RESULTS

Study selection

The search strategy retrieved 800 studies, of which 461 duplicates were removed; the remaining 339 studies were screened by title and abstract. Thirty-eight studies were identified for full-text review,and a final 24 studies (18 RCTs and 6 PSMs) comprising 5,132 patients were included (Fig. 1).

Study characteristics

Nine studies compared CBA with RFA,[22-31] 3 compared CBA with AAD,[32-34] 5 compared RFA with AAD,[35-39]

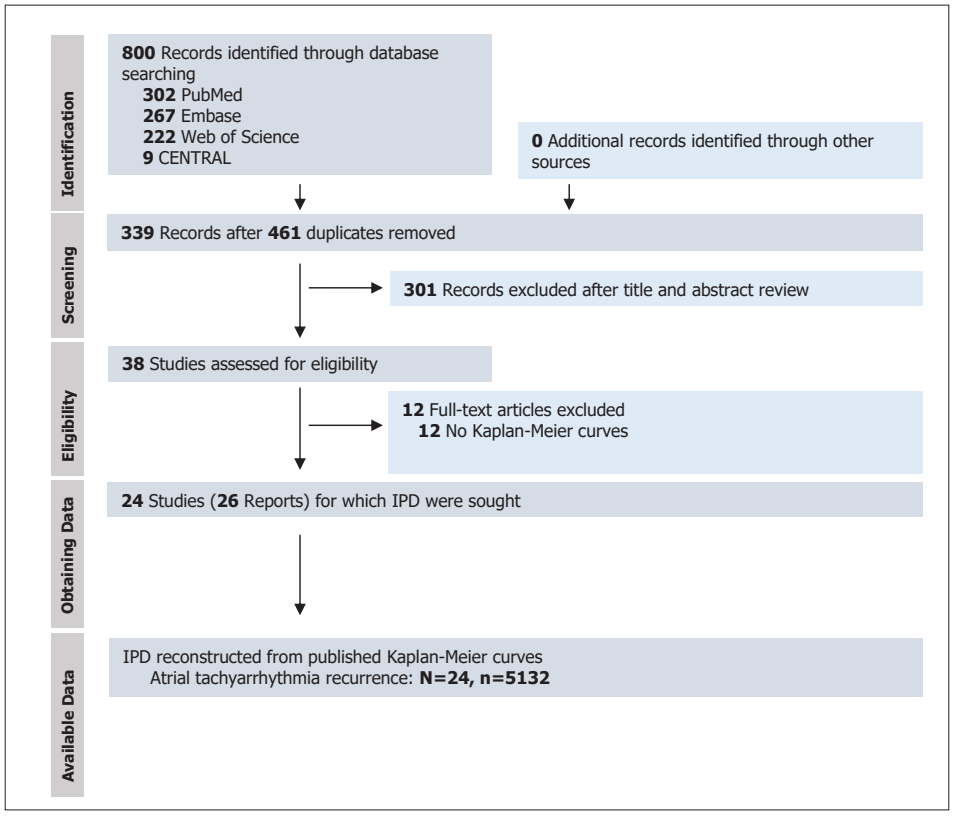


Fig. 1. PRISMA flowchart of included studies.

2 compared LBA with CBA,[40,41] 2 compared PVAC with RFA,[42,43] 1 compared HBA with CBA,[44] and 1 compared HBA with AAD.[45] The remaining study was a 3-way comparison of CBA, RFA and a combination of both (CBA + RFA)[46] (Table 1). A predominantly Caucasian, male population was involved, and the incidence of diabetes mellitus was under 25% (online Supplementary Table S2). The average duration of AF ranged from 0.4–8.6 years. Baseline beta-blocker use ranged from 5.8–67%. Only 1 study allowed AAD regimens to be newly initiated in the treatment arm.[35] In studies with an AAD arm, the most common AADs were flecainide and propafenone. Second-generation CBA was the most common subtype of CBA used in most studies, while studies with an RFA arm were mostly a mix of contact force and non-contact force subtypes. A blanking period, wherein AF recurrence after index ablation was not counted as treatment failure, was implemented in almost all studies, typically spanning 90 days. Adverse events are shown in the online Supplementary Table S3. There were no gross differences in serious adverse events between any ablation modality and AAD, or between ablation modalities, although studies were not likely powered to detect such differences. All studies were deemed to have a low risk of bias (online Supplementary Table S4).

Pairwise comparisons

Three or more studies reported direct comparisons for the following PAF treatments: CBA versus AAD, RFA versus AAD, and CBA versus RFA. IPD-derived one-stage Kaplan-Meier comparisons for the primary outcome among 3 studies showed a significant benefit of CBA over AAD (shared-frailty HR=0.44, 95% CI=0.35–0.56, P<0.001) (Fig 2A). RFA was also superior to AAD (shared-frailty HR=0.26, 95% CI=0.20–0.33, contact-force P<0.001) across 5 studies (Fig. 2B). There was no significant difference in the primary outcome between CBA and RFA (shared-frailty HR=0.91, 95% CI=0.80–1.04, P=0.174) across 10 studies (online Supplementary Fig. S1). Two-stage comparisons were concordant with one-stage comparisons (online Supplementary Figs. S2–4).

Frequentist network meta-analysis

The combined Kaplan-Meier plot of all studies is shown in Fig. 3 and the network plot of all included trials is shown in online Supplementary Fig. S5. Derived HRs of atrial tachyarrhythmia recurrence compared to AAD were 0.35 (95% CI=0.25–0.48) for CBA, 0.34 (95% CI=0.25–0.47) for RFA, 0.14 (95% CI=0.07–0.30) for CBA + RFA, 0.20 (95% CI=0.10–0.41) for HBA, 0.43 (95% CI=0.15–1.26) for LBA, and 0.33 (95% CI=0.18–0.62) for PVAC (Table 2 and online Supplementary Fig. S6). Hence, all treatments except LBA showed significant benefits compared to AAD for the primary outcome. Furthermore, CBA + RFA was significantly favoured over CBA (HR=0.41, 95% CI=0.20–0.83) and RFA (HR=0.41, 95% CI=0.21–0.83) but not against other modalities. Tests of heterogeneity (I^2=64%, Cochran's Q=52.8, P<0.001) indicated moderate between-study heterogeneity and justified the use of a random-effects model. P-scores ranked CBA + RFA as the best modality, followed by HBA (Table 3).

Restricted mean survival time network meta-analysis

When the pairwise comparison with the largest number of direct studies (CBA versus RFA) was analysed, the proportional hazards assumption was violated (online Supplementary Fig. S7). Hence, further analysis was performed using RMST-based NMAs. Separate RMST-R and RMST-D analyses both demonstrated that all ablation therapies were superior to AAD (online Supplementary Figs. S8–11, online Supplementary Tables S5 and S6), with RMST-R versus AAD ranging from 1.33–2.11 and RMST-D versus AAD ranging from 0.15–0.23 year. In the RMST-R analysis, CBA + RFA was significantly superior to all therapies except HBA. P-scores ranked CBA + RFA as the best therapy (Table 2).

Sensitivity analysis

When restricted to the 18 included RCTs only, the hazard ratio-based Frequentist NMA showed similar results to the entire cohort (online Supplementary Fig. S12, Supplementary Table S7). Moderate heterogeneity was observed (I^2=75%, Cochran's Q=51.3, P<0.001).

Network meta-analysis of procedural time

The NMA of procedural time across various therapies was found to have high heterogeneity and inconsistency between studies (I^2=92%, Cochran's Q=120, P<0.001). PVAC was ranked as the fastest procedure, followed by CBA; both had a significantly faster procedural time than RFA (online Supplementary Table S8, Supplementary Fig. S13). CBA + RFA had a significantly longer procedural time than all other ablation therapies.

DISCUSSION

Since the identification of focal origins of atrial ectopic beats and their successful ablation using radiofrequency energy,[7] subsequent modalities have aimed to achieve the same outcome via different methods of energy delivery. Alongside technical advancements such as contact force

Table 1. Characteristics of included studies

Study	Design	Country	Study period	Study size	Follow-up duration, months	Comparator arms	Blanking period, days	Inclusion criteria	Exclusion criteria
Ang 2018 Cryo vs RF	RCT	UK	Jul 2009–Dec 2012	203	≥18	CBA vs RFA vs CBA + RFA	90	>18 years, documented PAF on at least 2 occasions and accepted for catheter ablation for AF	Severe left atrial dilatation (>50mm), severe valvular disease, previous left atrial ablation, persistent AF, potentially reversible cause of AF, any contraindication to ablation
Buist 2018	RCT	Netherlands	NR	269	12	CBA vs RFA	90	Suitable for primo PVI for drug-refractory paroxysmal or early persistent AF	Procedures in which additional ablation strategies (e.g.complex fractionated atrial electrograms, linear ablations, right atrium ablations) were applied
Kuck 2018 FIRE AND ICE	RCT	8 countries	Jan 2012–Jan 2015	750	12	CBA vs RFA	90	18–75 years, symptomatic PAF with at least 2 episodes and at least one episode documented (30 seconds length, documented by ECG within last 12 months) that was refractory to class I or class III AADs or beta blockers	Life expectancy <1 year, pregnant or breastfeeding women, active systemic infection, cryoglobulinaemia, cardiac surgery/PCI/myocardial infarction in preceding 3 months, unstable angina pectoris, contraindication to chronic anticoagulation, NYHA class III-IV heart failure, LVEF <35%, mitral prosthesis, intracardiac thrombus
Andrade 2019/ Larsen 2020 CIRCA DOSE	RCT	Canada	Sep 2014–Jul 2017	346	12	CBA vs RFA	90	>18 years, PAF refractory to at least one class I or class III AAD	Previous left atrial ablation or surgery, AF due to reversible cause, intracardiac thrombus, cardiac valve prosthesis, contraindication to anticoagulation, clinically significant mitral valve regurgitation or stenosis, NYHA class III-IV heart failure, pregnancy, stroke/TIA in preceding 6 months, LVEF <35%
Pak 2021 CRAFT	RCT	South Korea	NR	312	12	CBA vs RFA	90	Patients who underwent catheter ablation for symptomatic and drug-refractory non-valvular PAF	Persistent or permanent AF, rheumatic valvular disease, significant structural heart disease other than left ventricular hypertrophy, left atrial diameter ≥55mm, history of AF ablation or cardiac surgery
Perez-Castellano 2014 COR	RCT	Spain	Jul 2009–Mar 2011	50	12	CBA vs RFA	90	18–75 years, symptomatic recurrent PAF (42 episodes in the last 6 months) refractory to ≥1 AADs (class I or III) and an anatomical pattern consisting of 4 single pulmonary veins	Prior AF ablation, prior cardiac surgery, moderate to severe valvular heart disease, anteroposterior left atrial diameter >50mm, hyperthyroidism, intracardiac thrombus, contraindications for anticoagulant therapy, concomitant acute illness, pregnancy, unavailability for follow-up for at least 1 year

Table 1. Characteristics of included studies (Cont'd)

Study	Design	Country	Study period	Study size	Follow-up duration, months	Comparator arms	Blanking period, days	Inclusion criteria	Exclusion criteria
Ikenouchi 2018	PSM	Japan	Jan 2012–Aug 2017	198	12	CBA vs RFA	90	Consecutive patients >75 years with PAF or persistent atrial fibrillation undergoing first PVI[a]	Left atrial thrombus, abnormal thyroid function, severe frailty, long-standing AF (>1 year), severe valvular heart disease, contraindications for the procedure
Knecht 2014 BEAT-AF	PSM	Switzerland	NR	142	12	CBA vs RFA	90	Consecutive patients with documented episodes of AF	Persistent or permanent AF, history of any previous left atrial procedure (surgical or percutaneous), use of a magnetic navigation system
Matta 2018	PSM	Italy	NR	92	12	CBA vs RFA	90	Consecutive patients suffering from paroxysmal atrial fibrillation treated with CBA or RFA	NR
Tokuda 2016	PSM	Japan	NR	246	12	CBA vs RFA	90	414 consecutive patients who had undergone an initial catheter ablation procedure for PAF	NR
Andrade 2020 EARLY AF	RCT	Canada	Jan 2017–Dec 2018	303	12	CBA vs AAD	90	>18 years with symptomatic AF and ≥1 episode of AF detected on ECG within 24 months before randomisation	History of daily use of a class I or class III AAD at therapeutic doses
Kuniss 2021 Cryo FIRST	RCT	20 sites worldwide	Apr 2014–Oct 2018	218	12	CBA vs AAD	90	18–75 years with a normal ECG, LVEF ≥50%, thickness of the inter-ventricular septum ≤12mm, left atrium diameter (short axis) <46mm, recurrent symptomatic PAF, drug naive (had not previously received a Class I or III AAD for >48 hours)	Persistent AF, previous left atrial ablation or cardiac surgery, documented typical atrial flutter, previous TIA or stroke, intracardiac thrombus, hypertrophic cardiomyopathy
Wazni 2020 STOP AF	RCT	US	Jun 2017–May 2019	203	12	CBA vs AAD	90	18–80 years with recurrent symptomatic PAF	Previous AAD treatment (class I or III) for ≥7 days, enlarged left atrial diameter (>5cm), previous left atrial ablation or left atrial surgical procedure
Kuck 2021 ATTEST	RCT	29 sites worldwide	Feb 2012–May 2018	255	36	RFA vs AAD	90	≥60 years of age with PAF for ≥2 years and with ≥2 episodes over the 6 months preceding enrolment	Reversible AF, previous diagnosis of persistent/permanent AF/AT, cardioversion >48 hours after onset of AF/AT, recent cardiovascular events

Table 1. Characteristics of included studies (Cont'd)

Study	Design	Country	Study period	Study size	Follow-up duration, months	Comparator arms	Blanking period, days	Inclusion criteria	Exclusion criteria
Morillo 2014 RAAFT-2	RCT	16 sites worldwide	Jul 2006–Jan 2010	127	24	RFA vs AAD	90	18–75 years, symptomatic with recurrent PAF lasting > 30 seconds (≤4 episodes within the prior 6 months); experienced at least 1 episode that was documented by surface ECG, 6 months before randomisation; and had no previous AADs	Previous AAD treatment, LVEF <40%, left atrial diameter >5.5 cm; moderate-to-severe left ventricular hypertrophy (wall thickness >1.5cm), valvular disease, coronary artery disease, or postcardiac surgery within 6 months; left heart ablation procedure, complete contraindication to use of heparin, warfarin, or both
Pappone 2011 APAF	RCT	Italy	Jan 2005–May 2005	198	48	RFA vs AAD	42	18–70 years, creatinine concentration <1.5mg/dL, AF history >6 months, AF burden >2 episodes/month in the last 6 months	AF secondary to transient or correctable abnormality, intra-atrial thrombus, tumour precluding catheter insertion, LA diameter >65mm, LVEF <35%, heart failure >NYHA functional class II, prior AAD therapy with amiodarone, flecainide, and sotalol, contraindication to beta-blocking therapy
Wazni 2005	RCT	3 countries	Dec 2001–Jul 2002	70	12	RFA vs AAD	None	18–75 years, monthly symptomatic AF episodes for at least 3 months	Previous history of atrial flutter or AF ablation, previous open-heart surgery, previous treatment with AAD, contraindication to long-term anticoagulation
Wilber 2010	RCT	19 sites worldwide	Oct 2004–Oct 2007	167	9	RFA vs AAD	90	3 symptomatic AF episodes (≥1 episode verified by ECG) within the 6 months before randomisation, not responding to ≥1 AAD (class I, class III, or atrioventricular nodal blocker)	AF ≥30 days in duration, age <18 years, LVEF <40%, previous ablation for AF, documented left atrial thrombus, amiodarone therapy in the previous 6 months, NYHA class III or IV, myocardial infarction within the previous 2 months, CABG in previous 6 months, thromboembolic event in previous 12 months, severe pulmonary disease, implanted ICD, contraindication to AAD or anticoagulants
Suruga 2021	PSM	Japan	Oct 2016–Aug 2017	60	12	HBA vs CBA	90	Consecutive HBA patients and PSM CBA patients	NR

Table 1. Characteristics of included studies (Cont'd)

Study	Design	Country	Study period	Study size	Follow-up duration, months	Comparator arms	Blanking period, days	Inclusion criteria	Exclusion criteria
Sohara 2016	RCT	Japan	NR	143	9	HBA vs AAD	84	20–75 years, refractory to ≥1 class I to IV AADs	Previous left atrial ablation or surgery for AF, refractory to selected AADs, NYHA class III–IV, myocardial infarction or unstable angina pectoris during the previous 6 months, comorbid severe ischaemic heart disease, valvular disorder, severe pulmonary hypertension, carotid occlusion, deep-vein thrombosis, history of cerebral infarction or intracerebral bleeding with apparent neurological symptoms during the previous 6 months
Chun 2021	RCT	Germany	Apr 2017–Apr 2019	200	12	LBA vs CBA	90	18–80 years, symptomatic PAF or persistent AF refractory to ≥1 AAD, including beta-blockers (class I–III)[a]	Previous PVI attempts. ineligible for treatment with oral anticoagulation, presence of an intracardiac thrombus, moderate or severe mitral valve disease
Yano 2021	PSM	Japan	Apr 2019–Jul 2020	74	3	LBA vs CBA	None	Consecutive PAF patients undergoing primary PVI with CBA or LBA	NR
Gal 2014	RCT	Netherlands	NR	460	43	PVAC vs RFA	90	Consecutive patients with symptomatic AF	NR
McCready 2014	RCT	UK	Sep 2007–Mar 2012	188	12	PVAC vs RFA	90	Patients with PAF who had failed at least one AAD who had been listed for a planned PVI procedure	Patient objection, prior AF ablation, left atrial size >60mm, mechanical prosthetic mitral valve replacement, hypertrophic cardiomyopathy, contraindications to anticoagulation, pregnancy

[a] Although persistent AF was included in the trial, only the paroxysmal AF subgroup was included in subsequent analysis.

AAD: antiarrhythmic drugs; AF: atrial fibrillation; AT: atrial tachycardia; CABG: coronary artery bypass graft; CBA: cryoballoon ablation; CBA + RFA: combined cryoballoon plus radiofrequency ablation; ECG: electrocardiogram; HBA: hot balloon ablation; ICD: implantable cardioverter-defibrillator; LA: left atrial; LBA: laser balloon ablation; LVEF: left ventricular ejection fraction; NR: not reported; NYHA: New York Heart Association; PAF: paroxysmal atrial fibrillation; PSM: propensity-score matched study; PVAC: pulmonary vein ablation catheter; PVI: pulmonary vein isolation; RCT: randomised controlled trial; RFA: radiofrequency ablation; TIA: transient ischaemic attack

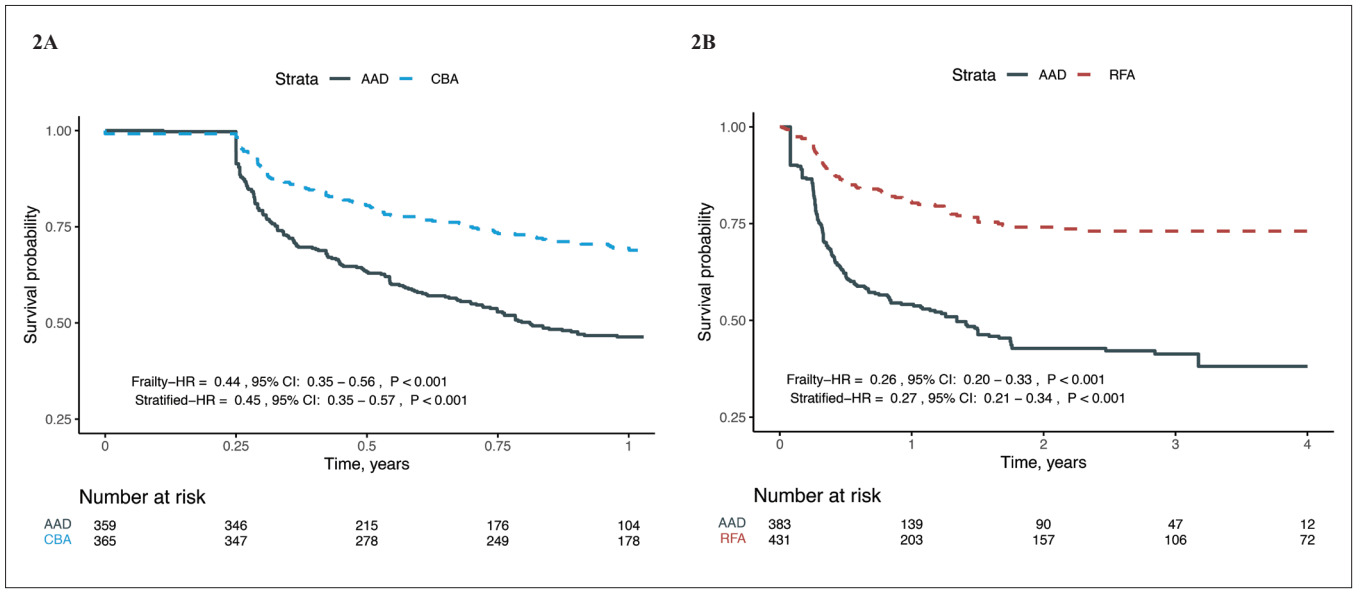


Fig. 2. Individual patient data one-stage meta-analysis of freedom from atrial tachyarrhythmias for (A) CBA versus AAD, (B) RFA versus AAD.
AAD: antiarrhythmic drugs; CBA: cryoballoon ablation; CI: confidence interval; HR: hazard ratio; RFA: radiofrequency ablation

ablation, which provides real-time feedback on tissue contact, and remote magnetic navigation, which allows mapping via stereotaxis, ablation has become increasingly safer and more efficacious.[47]

Accordingly, a meta-analysis of the relative efficacies of CBA versus RFA or ablation versus AAD has been previously performed.[11] However, this can only present fragmented viewpoints of the larger picture of ablation therapies for PAF. A recent NMA by Kukendrarajah et al.[48] compared CBA, RFA, LBA and PVAC across 14 RCTs, and concluded that the efficacy of non-RFA technologies was comparable to that of RFA. However, AAD was not included as a baseline comparator. Messori et al.[49] performed an RMST-based NMA between CBA, RFA and AAD, but only 5 RCTs were included in the analysis. Hence, there remained a role to synthesise all modalities from high-quality studies using IPD, which is recognised as the gold standard approach for evidence synthesis.[16]

This IPD-NMA was congruent with previous results in showing the significance of CBA and RFA over AAD in reducing AF recurrence. Pairwise IPD comparisons, which represent more robust analyses compared to pooled study-level aggregate data, showed a large divergence in Kaplan-Meier curves for both CBA and RFA compared to AAD, suggesting a sustained long-term benefit. The certainty of their benefit is further strengthened by indirect comparisons due to the large number of trials comparing CBA to RFA. Altogether, the clinically significant benefit of commonly used ablation therapies across all 3 NMA models, along with a similar safety and adverse event profile to AAD,

Table 2. League table comparing hazard ratios of various treatments in the hazard ratio-based Frequentist network meta-analysis

CBA + RFA						
0.41 (0.20–0.83)	CBA					
0.41 (0.21–0.83)	1.01 (0.79–1.29)	RFA				
0.70 (0.25–1.94)	1.71 (0.80–3.65)	1.69 (0.79–3.63)	HBA			
0.33 (0.09–1.13)	0.80 (0.29–2.21)	0.79 (0.28–2.25)	0.47 (0.13–1.66)	LBA		
0.43 (0.18–1.02)	1.04 (0.59–1.86)	1.03 (0.61–1.74)	0.61 (0.24–1.54)	1.30 (0.40–4.20)	PVAC	
0.14 (0.07–0.30)	**0.35 (0.25–0.48)**	**0.34 (0.25–0.47)**	**0.20 (0.10–0.41)**	0.43 (0.15–1.26)	**0.33 (0.18–0.62)**	AAD

AAD: antiarrhythmic drugs; CBA: cryoballoon ablation; CBA + RFA: combined cryoballoon plus radiofrequency ablation; HBA: hot balloon ablation; LBA: laser balloon ablation; PVAC: pulmonary vein ablation catheter; RFA: radiofrequency ablation

Bold text indicates values that crossed the threshold for significance

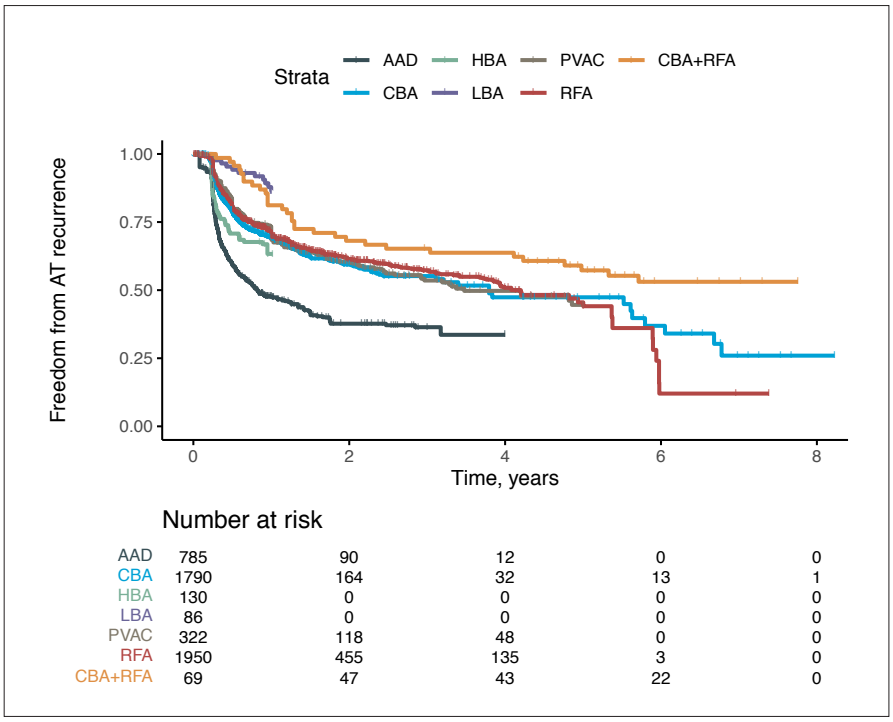


Fig. 3. Kaplan-Meier curves for atrial tachyarrhythmia recurrence, derived from reconstructed individual patient data from included studies.
AAD: antiarrhythmic drugs; AT: atrial tachyarrhythmia; CBA: cryoballoon ablation; CBA + RFA: combined cryoballoon plus radiofrequency ablation; HBA: hot balloon ablation; HR: hazard ratio; LBA: laser balloon ablation; PVAC: pulmonary vein ablation catheter; RFA: radiofrequency ablation

strengthens the case for upfront ablation therapy as a suitable alternative for patients who can tolerate the procedure. This NMA also provides Level 1A evidence for these comparisons, in support of prior observational studies that showed the benefit of ablation in reducing overall mortality and stroke,[50,51] and reinforcing current European Society of Cardiology guidelines,[5] which recommend both ablation and AAD as first-line treatment modalities for PAF depending on patient choice.

Moreover, the significance of these results can also be seen with CABANA, which is the largest RCT of upfront ablation versus AAD to date (2,204 patients in total).[52] Although only 43% of the CABANA cohort had paroxysmal AF (the rest had persistent or long-standing

Table 3. P-score rankings for various paroxysmal atrial fibrillation therapies

	Frequentist HR NMA	RMST-R NMA	RMST-D NMA
CBA + RFA	0.946	0.981	0.836
HBA	0.801	0.770	0.649
PVAC	0.492	0.419	0.482
RFA	0.460	0.429	0.482
CBA	0.444	0.434	0.492
LBA	0.348	0.465	0.552
AAD	0.011	0.002	0.007

Higher P-scores indicate greater estimated treatment efficacy. The top 3 treatments for each analysis are ranked with a colour gradient, with darker grey representing a higher P-score.

AAD: antiarrhythmic drugs; CBA: cryoballoon ablation; CBA + RFA: combined cryoballoon plus radiofrequency ablation; HBA: hot balloon ablation; HR: hazard ratio; LBA: laser balloon ablation; NMA: network meta-analysis; PVAC: pulmonary vein ablation catheter; RFA: radiofrequency ablation; RMST-D: restricted mean survival time difference; RMST-R: restricted mean survival time ratio

persistent AF), significant reductions in AF recurrence were seen (HR=0.52, 95% CI=0.45–0.60, $P<0.001$). No differences in mortality, death or cardiovascular hospitalisation were noted, but a lower-than-expected mortality rate in the AAD group may have contributed to the lower precision of the effect size estimate. CABANA was excluded from our analysis as the exact breakdown of RFA and CBA was not specified; however, severe adverse effect profiles were favourable with a 0.8% incidence of cardiac tamponade.

Within the modalities evaluate in this NMA, CBA and RFA showed similar outcomes in both pairwise and NMA comparisons. Previous RCTs have noted the relative ease of performing CBA compared to RFA, with CBA requiring more extensive fluoroscopic guidance.[23] This comparison is further complicated by the presence of newer technologies (contact force sensing and second-generation cryoballoon catheters), which were not well stratified within included studies to conduct a subgroup analysis. Contact force-guided catheters offer lower radiation exposure, procedural times, and cardiac perforation rates, but their association with other safety outcomes and clinical efficacy remains unclear.[53] Second-generation cryoballoons markedly decrease AF recurrence compared to the first generation.[54] A multicentre comparison of contact-force-guided RFA versus second-generation CBA found no significant difference in 18-month atrial arrhythmia freedom, with no periprocedural deaths in either group,[55] indicating that both are similarly safe and effective.

CBA + RFA was only performed in 1 included study,[46] involving RFA followed by 2 CBA freezes in a single procedure. The reported 5-year freedom from AF recurrence of 57%, and gross difference in Kaplan-Meier curves versus other techniques (Fig. 3), make it a frontrunner in this field. This was quantitatively supported by HR-based and RMST-R analyses, which found CBA + RFA significantly superior to CBA or RFA alone. CBA + RFA was associated with significantly fewer pulmonary vein reconnections (PVR) than CBA or RFA. Moreover, the different patterns of PVR observed in CBA and RFA—inferiorly for most of the former, superiorly for most of the latter[56]—are postulated to account for the synergy of combining both in a single procedure. Nonetheless, the NMA of procedural time found it significantly more time-consuming than all other ablation modalities. Accordingly, a more in-depth cost-benefit and safety-profile analysis of this technique is necessary, and more studies should be conducted in view of the current evidence for this technique being based solely on one RCT.

Studies of HBA only followed patients for up to 1 year. This lack of long-term follow-up may have led to the unexpected finding of HBA ranking second by way of *P* values within all 3 NMA methods. Plotting the results of all studies that used AAD as the control arm (online Supplementary Figs. S14 and S15), the AAD arm of Sohara et al.[45] had a much greater recurrence of atrial tachyarrhythmia than AAD arms in other studies. All patients in this study were refractory to 1 or more AADs upon enrolment, in contrast to some included studies[34,36] that excluded patients previously treated with an AAD. Combined with the slight variation in AADs used, it is possible that the relatively poor performance of the AAD arm in this study is a random error compounded by the low number of patients (n=43). Hence, the relatively inflated value of the HR for this study, which led to its high P-score ranking, may not be a true reflection of its efficacy. Nonetheless, HBA has been noted to have a more favourable learning curve compared to CBA,[57] which may render it a favourable starting point for centres without prior specialisation in ablation.

The remaining modalities, despite not being widely used, similarly showed significant benefits over AAD. PVAC is a modified form of RFA using a multielectrode, circular, bidirectional catheter; it may offer lower procedural times compared to conventional RFA but is no longer widely used due to concerns over the considerable levels of pulmonary stenosis after treatment.[58] LBA was significantly favoured over AAD in the RMST-based analyses but not the HR-based analysis, which may be attributed to the presence of only 2 LBA studies and its short follow-up. The visually guided LBA used was similar to RFA in requiring point-by-point ablations, as the aiming beam produces an arc covering only ~30° of a circle. LBA was ranked as the third-best modality by way of P-scores in both RMST analyses. The questionable ranking of HBA as the second-best therapy, as mentioned previously, may point to LBA being a stronger contender for second place. From Kaplan-Meier curves alone (Fig. 3), the trajectory of LBA resembles CBA + RFA—the highest-ranked modality—more than other modalities. A recent meta-analysis of LBA versus CBA suggested a trend towards higher 12-month procedural success for LBA,[59] but no head-to-head studies of LBA versus AAD have been performed. Hence, further trials with long-term follow-up are needed to fill these gaps in evidence.

Pulsed-field ablation (PFA) has emerged in recent years as a tool for pulmonary vein isolation. Nonetheless, promising outcomes in terms of myocardial tissue

specificity and dramatically lower procedural time, combined with a unique safety profile, have been found in single-arm trials.[60] Although one of the major points in favour of CBA usage is its lower procedural time, PFA may offer a promising alternative in the future. Further RCTs are needed to compare PFA to the myriad of technologies in this review.

Despite the use of IPD reconstruction as a rigorous statistical method that accounts for follow-up and censoring status, a noteworthy limitation was the inability to account for effects exerted by patient-level prognostic covariates on arrhythmia freedom. Moreover, all NMAs are limited by the assumptions of methodological equivalence and the similarity of baseline patient characteristics. Included studies were broadly similar in methodology barring the different study designs (RCT and PSM) which have been shown to be empirically equivalent to a large extent. Conversely, baseline patient characteristics varied considerably across studies —an inevitable limitation for essentially all NMAs. Several potential studies which provided Kaplan-Meier curves without risk tables were excluded, as graphical reconstruction is considerably less accurate without risk tables.[15] Measures of safety outcomes among studies were heterogeneous, and most were not sufficiently powered to detect differences in adverse effects; hence, a NMA of safety outcomes was also not feasible, although CABANA has shown favourable safety outcomes in a more adequately powered cohort.[52] Outcomes such as stroke, all-cause mortality, and periprocedural complications remain an important avenue for clinical decision-making, and future RCTs of individual ablation modalities should aim to be adequately powered for these outcomes as well. Cost-benefit analysis is also an important consideration, with catheter ablation as a whole shown to be reasonably cost-effective compared to AAD.[61] The results of this NMA, which quantitatively ranks 6 ablation techniques, provide a basis for a comprehensive cost-benefit analysis of individual ablation strategies.

CONCLUSION

In addressing the diverse field of ablation therapies for PAF using findings derived from robust networks of high-quality studies, this NMA found a consistent advantage of ablation therapies over AADs in preventing atrial tachyarrhythmia recurrence. Coupled with the large divergence of Kaplan-Meier curves in the CBA versus AAD, and RFA versus AAD pairwise comparisons, ablation represents a suitable first-line alternative to AAD for PAF in patients who are fit for the procedure. Intriguingly, the combination of CBA + RFA showed promising long-term superiority over conventional techniques, while LBA showed favourable short-term efficacy that may warrant a long-term investigation in future trials.

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