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Comparative efficacy and safety of catheter ablation interventions for atrial fibrillation: comprehensive network meta-analysis of randomized controlled trials

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Abstract

Purpose Point-by-point radiofrequency (RF) ablation has been the cornerstone of pulmonary vein isolation (PVI) for patients with atrial fibrillation (AF); however, it remains a complex and time-consuming procedure. Many novel AF catheter ablation (CA) techniques have been introduced, but whether they represent valuable alternatives remains controversial. Thus, we conducted a network meta-analysis to comprehensively evaluate the efficacy and safety of different CA interventions.

Methods We systematically searched several databases (Embase, PubMed, the Cochrane Library, and ClinicalTrials.gov) from inception to March, 2020. The primary outcomes of interest were freedom from atrial tachyarrhythmia (AT) and procedure-related complications; secondary outcomes included procedure time and fluoroscopy time.

Results Finally, 33 randomized controlled trials (RCTs) with a total of 4801 patients were enrolled. No significant differences were found among the different interventions in terms of primary efficacy or safety outcomes. PVAC was most likely to have the shortest procedure time (Prbest = 61.5%) and nMARQ the shortest fluoroscopy time (Prbest = 60.6%); compared with conventional irrigated RF (IRF) ablation, cryoballoon ablation (CBA) showed comparable clinical efficacy and safety; CBA with second-generation CB (CB2) had a significantly shorter procedure time than IRF with contact force technology (CF-IRF) (WMD = −20.75; $p = 0.00$).

Conclusion There is insufficient evidence to suggest that one CA technique is superior to another. However, PVAC may be associated with a shorter procedural duration, and the CB2 catheters also seemed to reduce the procedure time compared with that of CF-IRF. Further large-scale studies are warranted to compare the available CA techniques and provide an up-to-date optimum recommendation.

Keywords Atrial fibrillation · Catheter ablation · Network meta-analysis · Randomized controlled trials

1 Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is independently associated with an increased risk of stroke, heart failure, and cardiovascular morbidity [1]. Catheter ablation (CA) has been recommended for patients with symptomatic AF refractory to antiarrhythmic drugs, with pulmonary vein isolation (PVI) being the cornerstone of ablation procedures [2]. Point-by-point radiofrequency (RF) ablation has been applied to achieve PVI since 1998, and the success rate has approximately been 70% for patients with paroxysmal AF (PAF) after the first procedure [3]. Although point-by-point RF has been the cornerstone of CA and is widely used, it still remains a complex and time-consuming procedure and is highly operator dependent.

In recent years, several novel AF ablation techniques, mainly "single-shot-systems," have emerged, including the balloon-based techniques such as cryoablation ablation (CBA), hot balloon ablation (HBA), and laser balloon ablation (LBA); non-balloon multielectrode RF techniques such as nMARQ, mesh ablator (MA), and pulmonary vein ablation catheter (PVAC); and the high-power short-duration ablation

Xinbin Zhou, Jin Dai and Xiaoming Xu contributed equally to this work.

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technique. All of the alternative techniques intend to simplify the PVI procedure and reduce radiation exposure.

Although a number of studies have been performed to evaluate their efficacy and safety of these techniques, whether they represent valuable alternatives to the conventional irrigated RF (IRF) ablation remains controversial. Thus, we performed this network meta-analysis to assess the efficacy and safety of different CA intervention techniques based on the evidence from randomized controlled trials (RCTs).

2 Materials and methods

2.1 Search strategy and selection criteria

PubMed, Embase, the Cochrane Library, and ClinicalTrials.gov were systematically searched from their date of inception to March, 2020. The following terms and variants thereof were used: "atrial fibrillation," "cryoablation," "radiofrequency," "multi-electrode," "laser balloon," "hot balloon," and "high-power ablation." The references of the selected articles and relevant reviews were further reviewed for potentially relevant studies. To be included in our research, the studies were required to meet the following criteria: (1) RCTs, (2) published as a full-text article in English, (3) comparison between different CA interventions for AF patients, and (4) the outcomes of interest were reported.

2.2 Data collection and quality assessment

Data extraction and a quality assessment were performed independently by two investigators, and discrepancies were resolved by discussion and consensus. The following data were extracted: patients number, type of AF, participant characteristics, interventional strategy, duration of follow-up, and outcomes of interest. The quality of the included studies was assessed using the Cochrane Collaboration tool [4].

2.3 Primary and secondary outcomes

The primary efficacy outcome of interest was freedom from atrial tachyarrhythmia (AT) and without the administration of antiarrhythmic drugs (AADs) during follow-up. The primary safety outcome of interest was procedure-related complications. Secondary outcomes included procedure time and fluoroscopy time.

2.4 Statistical analysis

Continuous variables were described as median and standard deviation (SD) and categorical variables as *n* (%). For a conventional pairwise meta-analysis, STATA version 12.0 (STATA Corporation, TX, USA) was applied. The odds ratio (OR) and weighted mean difference (WMD) were calculated to demonstrate the overall result. The chi-square test was applied to estimate the heterogeneity across studies, and $I^2 > 50\%$ was considered indicative of significant heterogeneity. If there was significant heterogeneity, the possible causes were investigated and a random effects model was applied; otherwise, a fixed effects model was used. The publication bias for the pairwise meta-analysis was analyzed graphically with funnel plots and statistically using Egger's and Begg's tests.

For indirect and mixed comparisons, a Bayesian network meta-analysis was performed using R version 3.6.2 with R2WINBUGS and GeMTC packages computing OR or MD and their 95% credible intervals (CrIs). Markov chain Monte Carlo (MCMC) simulations were applied to estimate posterior probabilities with Gibbs sampling from at least 100,000 iterations. The probability of being the best treatment (Prbest) was estimated and ranked for each intervention. The node-splitting method was applied to assess network inconsistency.

3 Results

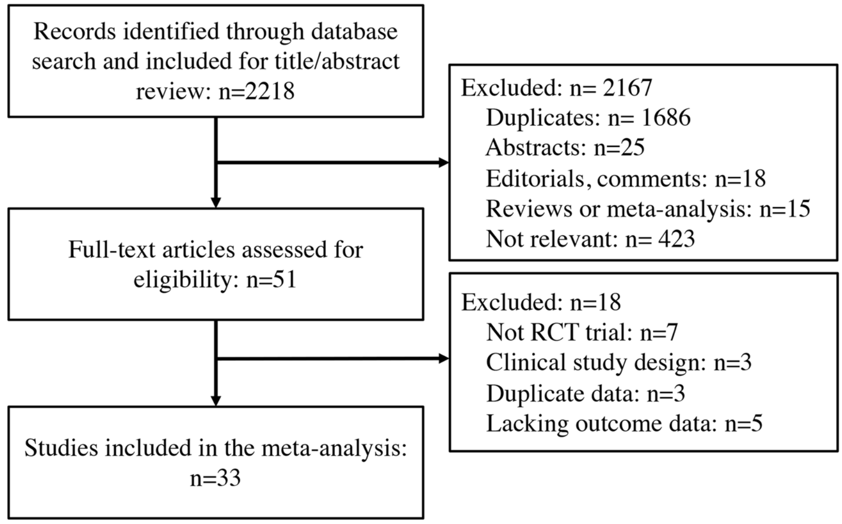
3.1 Eligible studies and characteristics

Thirty-three RCTs with a total of 4801 patients were finally included in this meta-analysis (Fig. 1). Six CA intervention strategies were evaluated, including conventional IRF, two kinds of balloon-based ablation strategies (CBA and LBA), two nonballoon multielectrode technologies (PVAC and nMARQ) and one basket-based technology (MA). There were no studies that meet the inclusion criteria for other CA strategies, such as hot balloon ablation or high-power ablation.

The baseline characteristics of the included studies are outlined in Table 1. Briefly, across the trials,15 studies compared CBA with IRF [5–19]; 2 studies compared CBA with MA [20, 21]; one study compared CBA with PVAC [22]; 7 studies compared PVAC with IRF [23–29]; 2 studies compared nMARQ with PVAC [30, 31]; one study compared nMARQ with IRF [32]; 3 studies compared LBA with IRF [33–35]; and 2 studies compared three interventions, including CBA, IRF, and LBA [36, 37]. The mean age of the patients ranged from to 52 to 67.5 years. Eight studies included both patients with paroxysmal AF (PAF) and persistent AF (PerAF) [8, 12, 18, 22, 27, 28, 30, 34], and the rest included only patients with PAF.

According to the Cochrane Collaboration tool [4], none of the included trials were thought to have a definite high risk of bias, and the study quality was adequate in most cases (Supplement Table 1). No significant publication bias was found with the funnel plot (Supplement Fig. 1) or revealed by the Begg's and Egger's tests based on the primary efficacy

Fig. 1 Flow chart of the systematic literature research



outcome of freedom from AT (Begg's test: $p = 0.556$, Egger's test: $p = 0.062$).

3.2 Primary endpoints

A pairwise meta-analysis was first performed, and results demonstrated that there were no significant differences among different interventions in terms of freedom from AT (comparisons including CBA vs. IRF, CBA vs. PVAC, CBA vs. MA, PVAC vs. IRF, nMARQ vs. PVAC, LBA vs. IRF, LBA vs. CBA, $p > 0.05$ for all). However, significant heterogeneity was detected for the comparison between CBA and IRF ($I^2 = 74.7\%$) (Fig. 2). Another pairwise meta-analysis was also conducted in terms of procedure-related complications; no significant difference was found among interventions, and no significant heterogeneity was detected (Fig. 3).

Further sensitivity analyses were conducted for the comparison for CBA vs. IRF depending on the type of cryoballoon/IFA catheter (first or second generation cryoballoon/with or without contact force technology) and type of AF patient (PAF or PerAF). The results showed that there were also no significant differences between CBA and IRF in terms of freedom from AT and complications when only patients with PAF were enrolled and analyzed (Supplement Fig. 2). There were also no significant differences between the second-generation cryoballoon (CB2) and contact force IRF (CF-IRF) or the first-generation cryoballoon (CB1) and no contact force IRF (nCF-IRF) regarding the primary endpoints (Supplement Fig. 3).

We then conducted a network meta-analysis to compare the six interventions (Fig. 4). The results indicated that LBA was most likely to be the best treatment for achieving the freedom from AT (Prbest = 36.7%), and nMARQ was most likely associated with the fewest procedure-related complications (Prbest = 76.1%). Both LBA and CBA had significantly more complications than both nMARQ (OR = 7.5 (95% CrCls, 1.0–72); OR = 7.2 (95% CrCls, 1.1–54); $p < 0.05$, respectively) and PVAC (OR = 3.9 (95% CrCls, 1.1–18); OR = 3.7 (95% CrCls, 1.3–12); $p < 0.05$, respectively (Tables 2 and 3). Consistency of the network analyses was satisfactory as the results from consistent and inconsistent Bayesian models were similar.

3.3 Secondary endpoints

The pairwise meta-analysis showed that there were no significant differences between CBA and IRF concerning procedure or fluoroscopy time (WMD = − 8.55 min, $p = 0.131$; WMD = 2.51 min, $p = 0.259$, respectively), whereas significant heterogeneities were detected ($I^2 = 93.5$ and 94.5%, respectively). Further analysis found that CBA with CB2 had a significantly shorter procedure time than CF-IRF (WMD = − 20.75 (95% CI, − 25.44 to − 16.06); $p = 0.00$), whereas no such difference was seen between CB1 and nCF-IRF ($p = 0.95$).

In terms of fluoroscopy time, there were no significant differences between CB2 and CF-IRF or CB1 and nCF-IRF ($p > 0.05$) (Supplement Fig. 3). PVAC had significantly both shorter procedure and fluoroscopy times compared with IRF (WMD = − 58.59 (95% CI, − 75.16 to − 42.02); $p = 0.00$ and WMD = − 9.58 (95% CI, − 16.82 to −2.34); $p = 0.01$, respectively).

In the comparison between different multielectrode technologies, nMARQ had shorter procedure and fluoroscopy times than PVAC (WMD = − 13.86 (95% CI, − 23.16 to − 4.57); $p = 0.003$; WMD = − 7.81 (95% CI, − 12.33 to − 3.30); $p = 0.001$, respectively). In addition, IRF was found to have shorter procedure and fluoroscopy times than LBA (WMD = 24.42 (95% CI, 1.42–47.43); $p = 0.037$ and WMD = 9.17 (95% CI, 0.09–18.26); $p = 0.048$, respectively). CBA was also found to have a shorter procedure time than

Table 1 The baseline characteristics of the included studies

Study	Year	Patients (*n*)		Strategy	Mean age (years)	Male (%)	Mean LAd (mm)	Mean LVEF (%)	Hypertention (%)	DM (%)	CAD (%)	Follow-up (months)
		PAF	PerAF									
Andrade	2019	327	19	CBA vs. IRF	59	67	37.8	59.2	34.7	NR	7.2	12
You	2019	140	0	CBA vs. IRF	58.6	56.4	NR	NR	56.5	17.9	NR	12
Giannopoulos	2019	120	0	CBA vs. IRF	60	NR	40.5	60	49.2	12.5	6.7	6
Bin Waleed	2019	58	0	CBA vs. IRF	61.8	68	36.2	59	54	10	NR	6
Davtyan	2018	89	0	CBA vs. IRF	56.6	46.1	4.1	NR	77.5	9	6.7	12
Buist	2018	229	40	CBA vs. IRF	58.9	71	NR	NR	40.8	23	NR	12
Watanabe	2018	52	0	CBA vs. IRF	65	72	40.5	60.5	60	16	NR	12
Gunawardene	2018	60	0	CBA vs. IRF	59.7	70	NR	59.5	55	NR	NR	12
Kuck	2016	762	0	CBA vs. IRF	60	60.9	40.7	NR	58.1	7.9	8.4	18
Hunter	2015	155	0	CBA vs. IRF	58.5	66.5	42.5	NR	32.3	5.8	7.7	12
Luik	2015	315	0	CBA vs. IRF	61	60.6	NR	NR	64.2	9.8	12.4	12
Perez-Castellano	2014	50	0	CBA vs. IRF	57	78	42	NR	28	12	NR	12
Schmidt	2013	99	0	CBA vs. IRF vs. LBA	63	NR	41	58	70	6	18	12
Pokushalov	2013	80	0	CBA vs. IRF	56	80	47	57.5	16.3	6.3	NR	12
Herrara	2012	38	22	CBA vs. IRF	56	80	40.7	NR	45	NR	11.7	12
Casella	2014	110	0	CBA vs. IRF vs. LBA	57	76	42.1	61.9	36%	NR	NR	12
Tse	2005	30	0	CBA vs. IRF	52	76.7	3.9	57	16.7	NR	3.3	12
Malmborg	2013	76	34	CBA vs. PVAC	60.5	75.5	41	NR	51.8	NR	9.1	12
Koch	2012	32	0	CBA vs. MA	61.7	59.3	NR	66.9	50	12.5	21.9	12
Schirdewan	2017	37	0	CBA vs. MA	63	59.5	NR	65.9	54.1	13.5	21.6	12
Keçe F	2019	70	0	PVAC vs. IRF	61	61.5	39.5	NR	48.6	4.3	14.3	12
Boersma	2016	120	0	PVAC vs. IRF	57	75	40.5	NR	NR	NR	NR	12
Podd	2015	50	0	PVAC vs. IRF	67.5	44	38.5	61	42	4	6	12
McCready	2014	188	0	PVAC vs. IRF	62	62	38	63	NR	9	NR	12
Gal	2014	377	83	PVAC vs. IRF	56.3	75.4	41	NR	35	6.5	NR	12
Bittner	2011	44	36	PVAC vs. IRF	58	64	42.5	NR	58.8	7.5	NR	8.5
Bulava	2010	102	0	PVAC vs. IRF	57.6	66.7	40.3	68.6	32	10	5	7
Sugihara	2018	50	0	nMARQ vs. PVAC	66	38	NR	NR	54	12	16	12
Kozluk	2019	71	31	nMARQ vs. PVAC	57	68.6	42	60	64.7	4.9	7.8	NR
Grimaldi	2017	68	0	nMARQ vs. IRF	63.2	59.6	NR	NR	61.8	7.4	NR	12
Ücer	2018	50	0	LBA vs. IRF	62.5	50	43.1	60.8	80	22	26	NR
Schmidt	2017	0	134	LBA vs. IRF	66	63	43	61	72.4	9.7	18.7	12
Dukkipati	2015	353	0	LBA vs. IRF	59.9	66.4	40	60.4	58.8	12.6	20.8	12

PAF, paroxysmal atrial fibrillation; *PerAF*, persistent atrial fibrillation; *LAd*, left atrial diameter; *LVEF*, left ventricular ejection fraction; *DM*, diabetes mellitus; *CAD*, coronary artery disease; *NR*, not reported; *LBA*, laser balloon ablation; *nMARQ*, nMARQ ablation; *CBA* , cryoballoon ablation; *PVAC*, pulmonary vein ablation catheter; *IRF*, irrigated radiofrequency ablation; *MA*, mesh ablator

LBA (WMD = 20.0 (95% CI, 4.75–35.25); $p = 0.01$), as well as a shorter fluoroscopy time than PVAC (WMD = − 15.0 (95% CI, − 21.17 to − 8.83); $p = 0.00$) (Figs. 5 and 6). Similar results were found when only patients with PAF were analyzed (Supplement Fig. 2).

Additional network analyses for the secondary endpoints were conducted and indicated that PVAC was most likely to have the shortest procedure time (Prbest = 61.5%) and that nMARQ may have the shortest fluoroscopy time (Prbest = 60.6%). The consistency of the

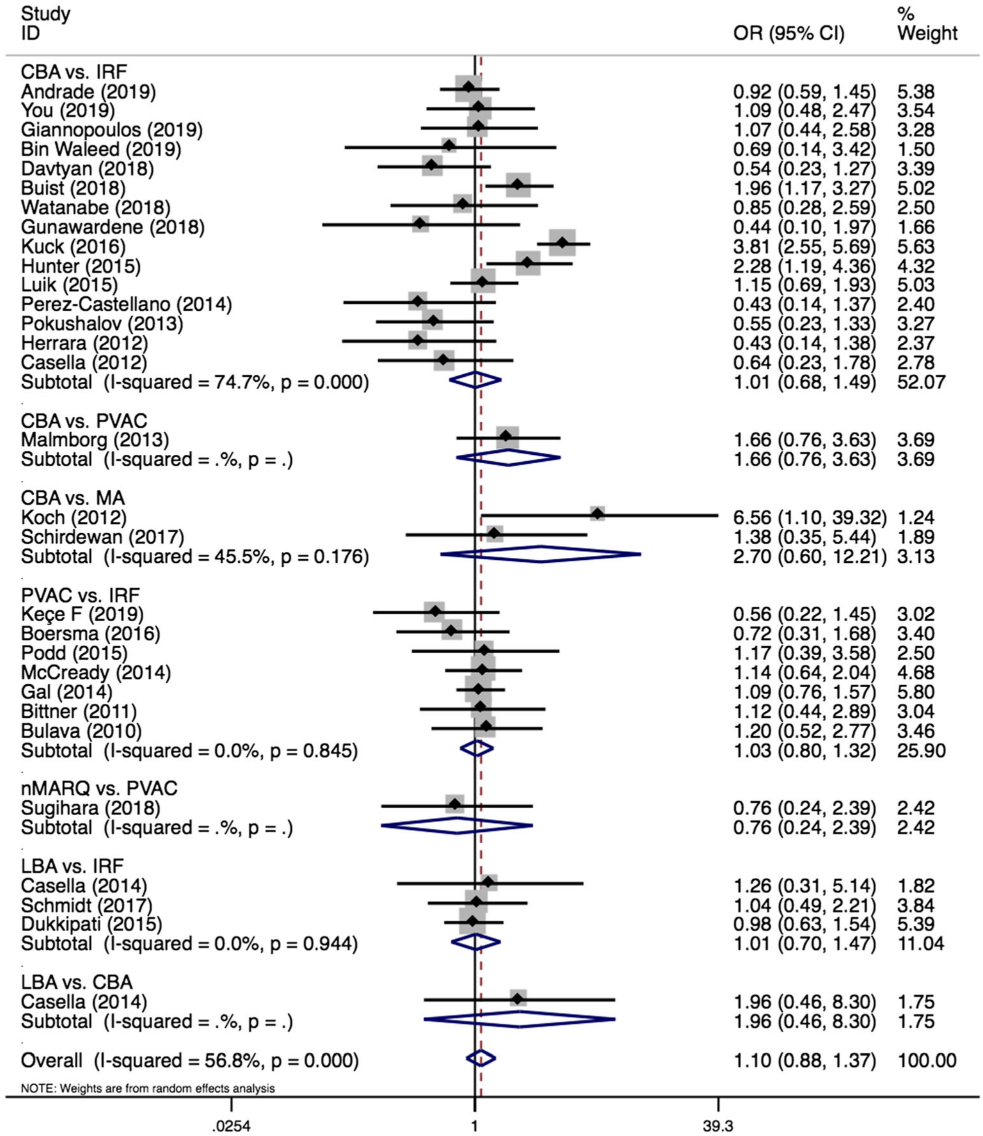


Fig. 2 Pairwise meta-analysis for the outcome of freedom from AT. AT, atrial tachyarrhythmia; OR, odds ratio; LBA, laser balloon ablation; nMARQ, nMARQ ablation; CBA, cryoballoon ablation; PVAC, pulmonary vein ablation catheter; IRF, irrigated radiofrequency ablation; MA, mesh ablator

network analyses for secondary outcomes was also satisfactory (Tables 4 and 5).

4 Discussion

4.1 Principal findings

To the best of our knowledge, this may be the first study to simultaneously compare 6 different CA techniques using a network meta-analysis based on evidence from RCTs. The main findings are as follows: (1) no significant differences were found among the different interventions in terms of freedom from AT or procedure-related complications; (2) PVAC seemed to be associated with a shorter procedure time than that of other techniques; and (3) compared with IRF, CBA had comparable efficacy and safety, while CB2 had a significantly shorter procedure time than CF-IRF.

4.2 Efficacy

A number of previous studies have evaluated efficacy of the “single-shot” approaches in comparison with a “point-by-point” technique such as IRF for PVI, but no consensus has been reached so far. These “single-shot” technologies have advantages of simplifying the PVI procedure by placing the ablation catheter at the antrum/ostium of the PV instead of continuous repositioning.

Based on evidence from both conventional meta-analyses and network analyses, we found no significant differences in terms of the freedom from AT among various interventions, which is consistent with a previous

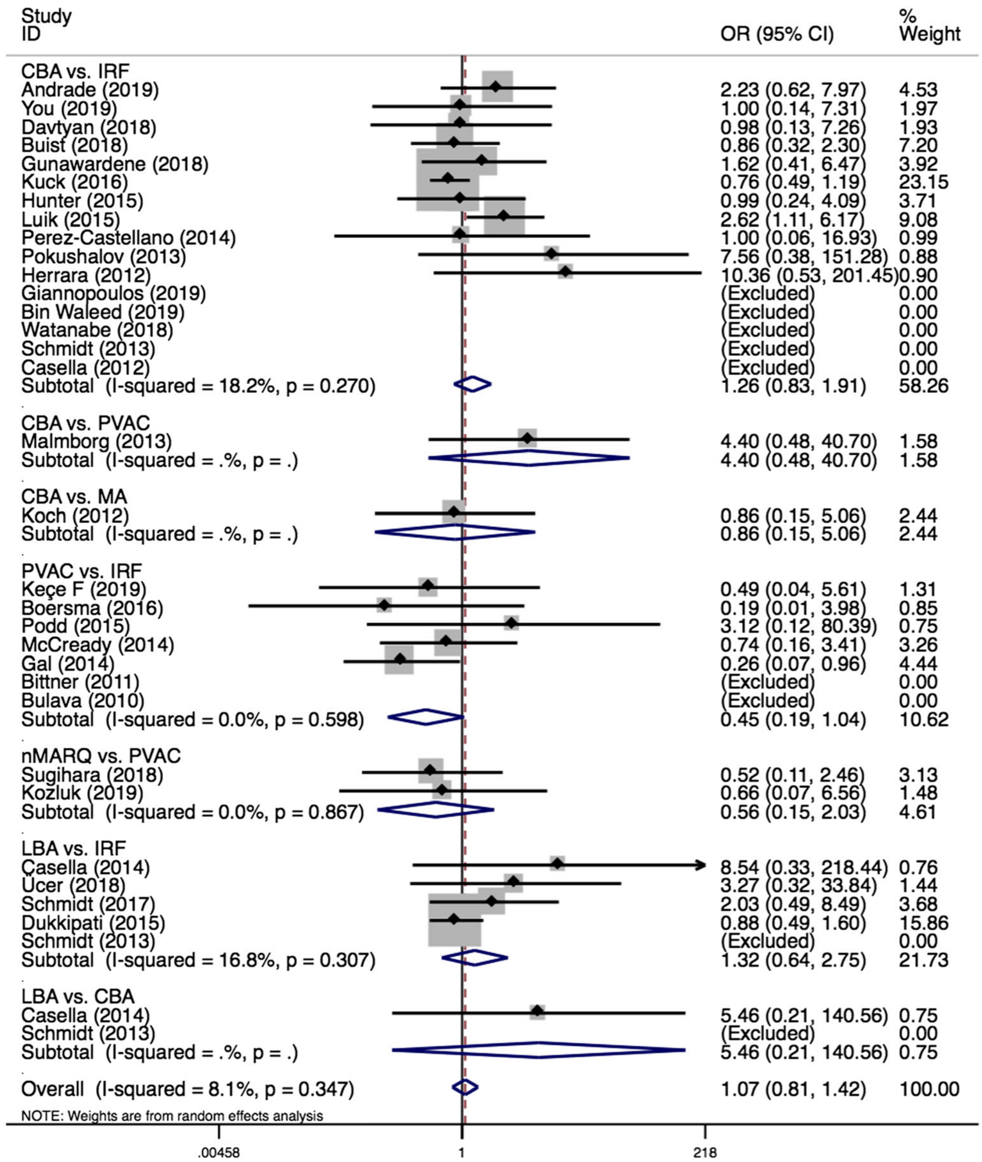


Fig. 3 Pairwise meta-analysis for the outcome of procedure-related complications. OR, odds ratio; LBA, laser balloon ablation; nMARQ, nMARQ ablation; CBA, cryoballoon ablation; PVAC, pulmonary vein ablation catheter; IRF, irrigated radiofrequency ablation; MA, mesh ablator

Table 2 Estimated differences based on the outcome of freedom from AT

Treatment	LBA	nMARQ	CBA	PVAC	IRF	MA
LBA	Prbest = 36.7%	0.69 (0.17–2.6)	0.97 (0.54–1.6)	0.91 (0.49–1.6)	0.95 (0.57–1.5)	0.34 (0.09–1.2)
nMARQ	–	Prbest = 22.3%	1.4 (0.39–5.2)	1.3 (0.39–4.7)	1.4 (0.40–5.1)	0.5 (0.08–2.9)
CBA	–	–	Prbest = 19.6%	0.94 (0.65–1.4)	0.98 (0.80–1.3)	0.36 (0.10–1.1)
PVAC	–	–	–	Prbest = 10.8%	1.0 (0.77–1.5)	0.38 (0.11–1.2)
IRF	–	–	–	–	Prbest = 8.4%	0.36 (0.10–1.1)
MA	–	–	–	–	–	Prbest = 2.2%

Results are expressed as OR with 95% CrCls in parentheses. Interventions are ordered according to efficacy ranking of the probability of being the best treatment (Prbest). OR > 1 indicates the intervention listed in the top row is more beneficial than the one in the left column

AT, atrial tachyarrhythmia; *LBA*, laser balloon ablation; *nMARQ*, nMARQ ablation; *CBA*, cryoballoon ablation; *PVAC*, pulmonary vein ablation catheter; *IRF*, irrigated radiofrequency ablation; *MA*, mesh ablator

Table 3 Estimated differences based on the outcome of procedure-related complications

Treatment	nMARQ	PVAC	MA	IRF	LBA	CBA
nMARQ	Prbest = 76.1%	1.9 (0.40–10)	8.4 (0.44–170)	4.9 (0.78–35)	*7.5 (1.0–72)*	*7.2 (1.1–54)*
PVAC	–	Prbest = 17.8%	4.4 (0.39–5.2)	2.6 (0.98–7.1)	*3.9 (1.1–18)*	*3.7 (1.3–12)*
MA	–	–	Prbest = 5.0%	0.59 (0.06–5.8)	0.91 (0.08–11.0)	0.85 (0.10–8.0)
IRF	–	–	–	Prbest = 0.5%	1.5 (0.65–4.7)	1.4 (0.88–2.6)
LBA	–	–	–	–	Prbest = 0.4%	0.96 (0.30–2.6)
CBA	–	–	–	–	–	Prbest < 0.2%

Results are expressed as OR with 95% CrCls in parentheses. Interventions are ordered according to efficacy ranking of the probability of being the best treatment (Prbest). OR > 1 indicates high risk and the intervention listed in the left column is more beneficial than the one in the top row. Values set in italics indicate that the difference was statistically significant

LBA, laser balloon ablation; *nMARQ*, nMARQ ablation; *CBA*, cryoballoon ablation; *PVAC*, pulmonary vein ablation catheter; *IRF*, irrigated radiofrequency ablation; *MA*, mesh ablator

study showing that endocardial PVI has similar outcomes regardless of the technique used [38].

Among these approaches, CBA and LBA are both balloon-based techniques. The visually guided LBA has been commercially available in Europe since 2009 and has been demonstrated to be noninferior compared with IRF for paroxysmal AF in large-scale RCTs [35]. In addition, the lesions created with laser energy were all found to be circumferential and transmural, which may lead to a low reconnection rate after PVI [33].

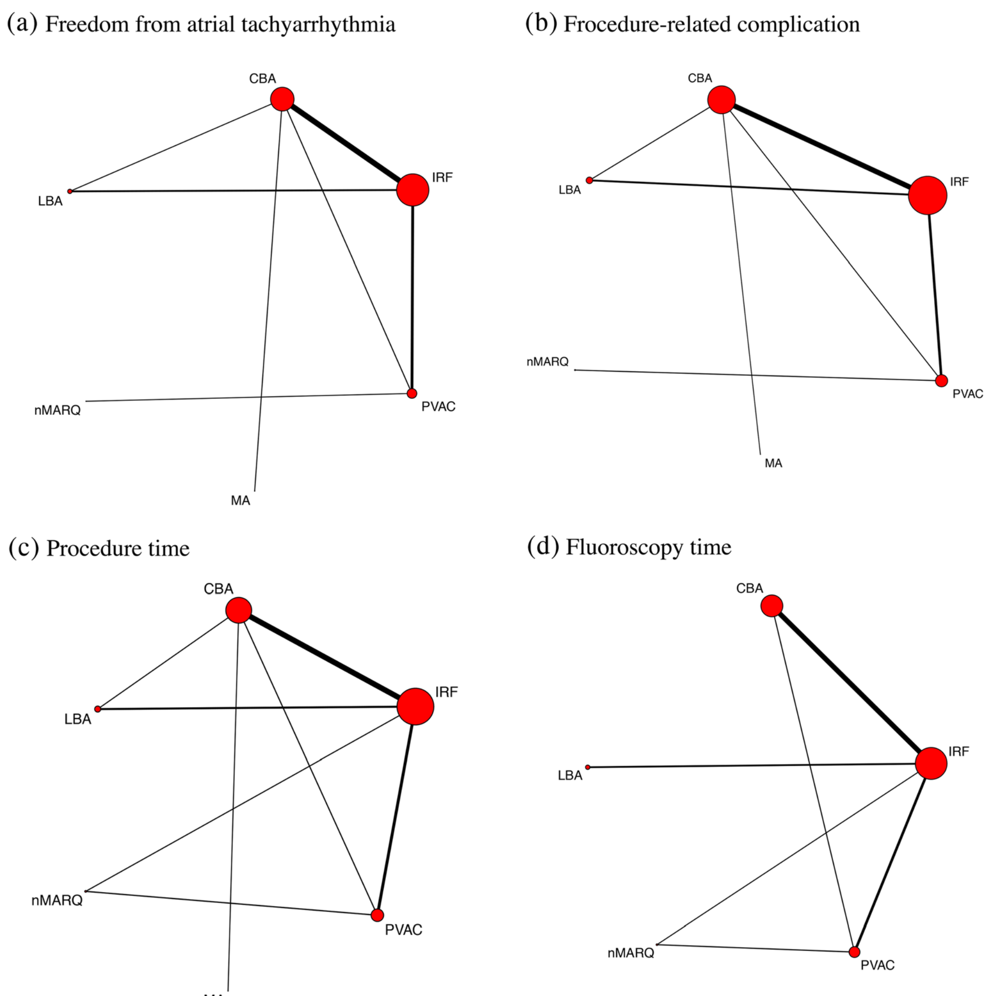


Fig. 4 Network of comparisons included in the analyses. The size of every circle is proportional to the number of randomly assigned patients and indicates the sample size. The thickness of the line corresponds to the number of trials. LBA, laser balloon ablation; nMARQ, nMARQ ablation; CBA, cryoballoon ablation; PVAC, pulmonary vein ablation catheter; IRF, irrigated radiofrequency ablation; MA, mesh ablator

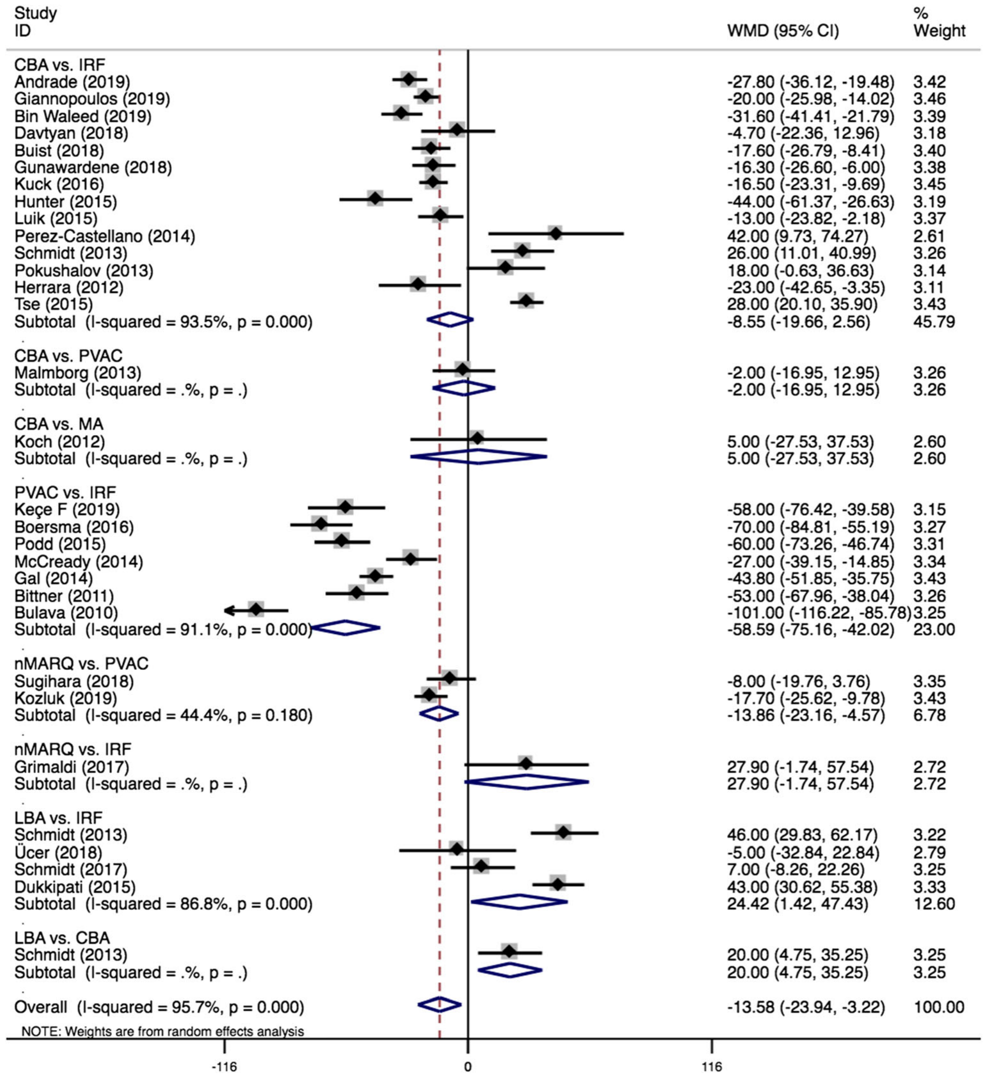


Fig. 5 Pairwise meta-analysis for the outcome of procedure time. WMD, weighted mean difference; LBA, laser balloon ablation; nMARQ, nMARQ ablation; CBA, cryoballoon ablation; PVAC, pulmonary vein ablation catheter; IRF, irrigated radiofrequency ablation; MA, mesh ablator

Regarding CBA, it is currently the most common alternative intervention for IRF, and the second-generation cryoballoon has also been introduced to address issues with abnormal PV anatomy. Both the pairwise and network meta-analyses demonstrated that cryoballoons have comparable efficacy with IRF, regardless of the type of CB (CB1 or CB2) or type of IRF (CF or nCF). These results are consistent with recently published meta-analyses and the largescale Fire and ICE trial [13]. However, significant heterogeneity was detected in the comparison between CBA and IRF for the efficacy outcome, and further sensitive analyses showed similar outcomes, whereas a comparison between CB2 and IRF was not available due to the lack of data.

Compared with IRF, CBA has a relatively high risk of phrenic nerve palsy, but it may also reduce the risk of cardiac tamponade and represents a valuable alternative for PVI.

PVAC and nMARQ are both circular, multielectrode catheters. PVAC is based on the nonirrigated duty-cycled ablation phased RF technology, and nMARQ is an irrigated, multielectrode electroanatomically guided catheter; despite their supposed clinical effectiveness both in our study and previous studies, the issue of safety remains a major concern [39, 40]. It should be noted that the nMARQ catheter was recalled from clinical use and a redesigned prototype is under evaluation [41]. Meanwhile, the recently introduced PVAC-GOLD catheter is also being re-evaluated, which may subsequently alter the risk-benefit profile [41].

The basket-based MA catheter was found to have the lowest Prbest ratio (2.2%), which has been shown in other studies in comparison with LBA. The MACPAF study revealed that complete PVI was not achieved in any of the MA groups, compared with 75% in the LBA

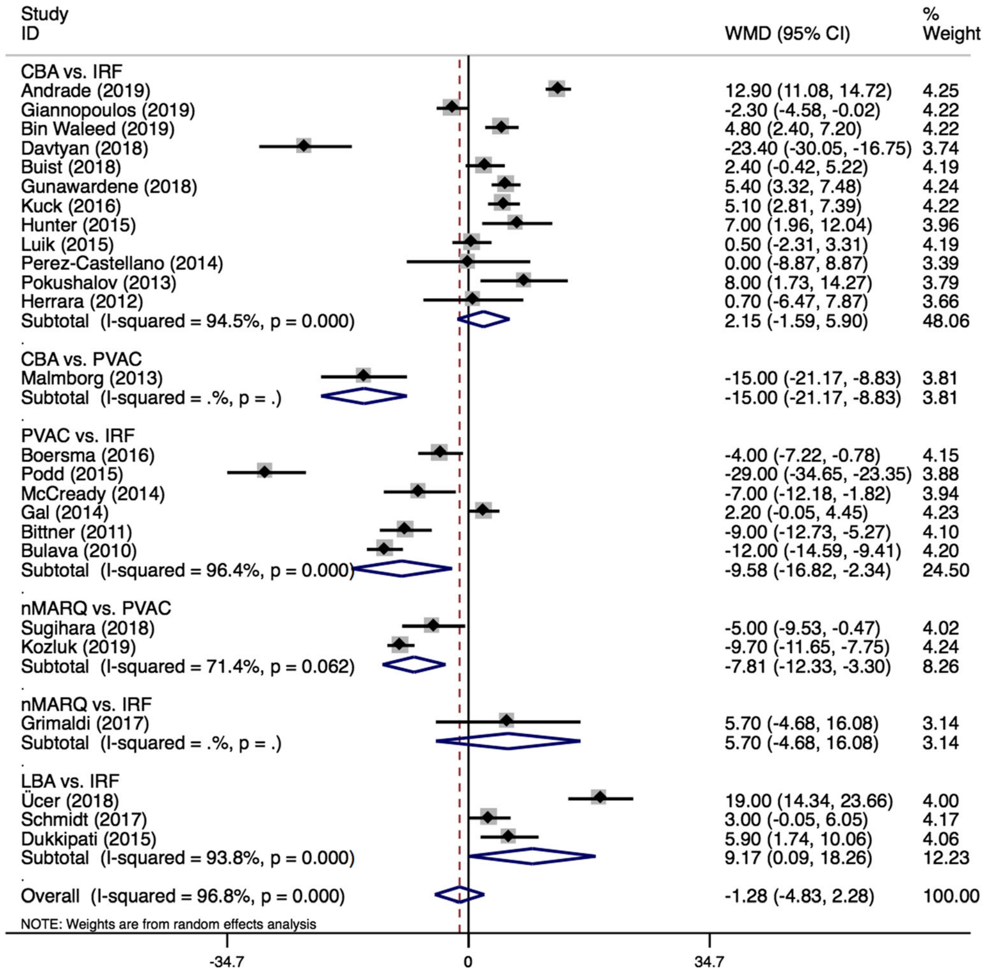


Fig. 6 Pairwise meta-analysis for the outcome of fluoroscopy time. WMD, weighted mean difference; LBA, laser balloon ablation; nMARQ, nMARQ ablation; CBA, cryoballoon ablation; PVAC, pulmonary vein ablation catheter; IRF, irrigated radiofrequency ablation; MA, mesh ablator

group [21], and other studies showed that only 18–36% of all MA patients could maintain sinus rhythm at 6–12 months follow-up; thus, this approach may not be recommended due to the insufficient efficacy [42].

4.3 Safety

The prevalence of major complications varies widely, from 0.8 to 16.3% according to the previous studies [2, 43–45]. In our study, comparable risk estimates for procedure-related

Table 4 Estimated differences based on the outcome of procedure time

Treatment	PVAC	nMARQ	MA	CBA	LBA	IRF
PVAC	Prbest = 61.5%	12.0 (− 22.0 to 47.0)	30.0 (− 38.0 to 99.0)	*35.0 (11.0–59.0)*	*66.0 (31.0–100)*	*46.0 (26.0–66.0)*
nMARQ	–	Prbest = 21.2%	19.0 (− 57.0 to 94.0)	24 (− 16.0 to 62.0)	*54.0 (7.2–100.0)*	35.0 (− 3.0 to 71.0)
MA	–	–	Prbest = 17.2%	4.9 (− 59.0 to 69.0)	36.0 (− 36.0 to 110)	16.0 (− 50.0 to 82.0)
CBA	–	–	–	Prbest = 0.09%	31.0 (− 0.14 to 61.0)	11.0 (− 3.9 to 26.0)
LBA	–	–	–	–	Prbest = 0.02%	− 20.0 (− 48.0 to 8.6)
IRF	–	–	–	–	–	Prbest = 0.00%

Results are expressed as mean difference with 95% CrCls in parentheses. Interventions are ordered according to efficacy ranking of the probability of being the best treatment (Prbest). Negative number indicates that the intervention listed in the top row is more beneficial than the one in the left column. Values set in italics indicate that the difference was statistically significant

LBA, laser balloon ablation; *nMARQ*, nMARQ ablation; *CBA*, cryoballoon ablation; *PVAC*, pulmonary vein ablation catheter; *IRF*, irrigated radiofrequency ablation; *MA*, mesh ablator

Table 5 Estimated differences based on the outcome of fluoroscopy time

Treatment	nMARQ	PVAC	CBA	IRF	LBA
nMARQ	Prbest = 60.6%	2.3 (− 11.0 to 15.0)	7.4 (− 8.1 to 23.0)	7.0 (− 7.3 to 21.0)	16.0 (− 3.0 to 35.0)
PVAC	–	Prbest = 30.4%	5.1 (− 4.7 to 15.0)	4.8 (− 3.4 to 13.0)	14.0 (− 1.1 to 29.0)
CBA	–	–	Prbest = 5.2%	− 0.32 (− 6.4 to 5.9)	8.9 (− 5.2 to 23.0)
IRF	–	–	–	Prbest = 2.4%	9.2 (− 3.4 to 22.0)
LBA	–	–	–	–	Prbest = 1.2%

Results are expressed as mean difference with 95% CrCls in parentheses. Interventions are ordered according to efficacy ranking of the probability of being the best treatment (Prbest). Negative number indicates that the intervention listed in the top row is more beneficial than the one in the left column. Values set in italics indicate that the difference was statistically significant

LBA, laser balloon ablation; *nMARQ*, nMARQ ablation; *CBA*, cryoballoon ablation; *PVAC*, pulmonary vein ablation catheter; *IRF*, irrigated radiofrequency ablation; *MA*, mesh ablator

major complications were found between different ablation techniques.

Previous studies have demonstrated the differences in the risk profiles of different ablation technologies [13]; for example, a high risk of pericardial injury for IRF, phrenic nerve palsy (PNP) for LBA, thromboembolic events and PV stenosis for PVAC, and esophageal-atrial fistula for nMARQ.

PVAC was reported to be associated with a 1.48 times higher risk of silent cerebral embolism compared with IRF and CBA [46, 47], and its unknown impact on long-term cognitive function still remains a concern. Recently, the redesigned PVAC GOLD was found to have a similar safety profile, but with lower complication rates [48]. However, one should note that the results may be overshadowed by a high background rate of silent cerebral events, which may not be catheter-specific, as previous studies have shown that asymptomatic cerebrovascular emboli is common, with an incidence of 11–14% [41, 49]. As was different from PVAC, the later continuous irrigated forms of multiple electrode catheters, such as nMARQ, were thought to help reduce the risk of thrombus formation and, consequently, the incidence of cerebral microembolism [50].

Although the network analysis revealed that nMARQ and PVAC may be associated with less absolute complication numbers, especially compared with LBA and CBA, their complications were more severe and life-threatening, which is also why nMARQ was recalled for further investigation after early studies [39, 51].

PNP is a common complication of CBA; however, it is usually transient, and persistent PNP is only seen in < 1% of patients [52]. The recently introduced second-generation CBA was reported to have greater PVI efficacy, but at the same time, a higher incidence of transient PNP, possibly due to the larger cooling surface area and deeper damaged foci [53–56].

From the present analysis, we did not detect any best technique in terms of safety, and as the definition of procedure-related complications mostly lacked in the designs, the outcomes were relatively heterogeneous among the included studies. Thus, the individual risk profile should be taken into account when selecting CA energy sources, as the procedure-related complications may to a large extent be related to individual characteristics, operator experiences, and other procedural factors.

4.4 Secondary endpoints

In the current report, we found that fluoroscopy times were comparable among techniques, and PVAC may be associated with a shorter procedure time according to the network analysis. This is not surprising, as the "one-shot" techniques may require less catheter manipulation than point-by-point CA strategies such as IRF. The shorter procedure duration could lead to a more cost-effective approach for hospitals, as well as for patients with impaired heart function. However, the results became controversial when the pairwise meta-analysis was conducted. For example, the conventional meta-analysis demonstrated that nMARQ had shorter procedure and fluoroscopy times than PVAC, and IRF was found to have shorter procedure and fluoroscopy times than LBA. Possible explanations may be the heterogeneities between studies and between different comparisons. In terms of the secondary endpoints, nMARQ performed better than PVAC and PVAC performed better than IRF. However, when compared with IRF, nMARQ displayed a trend towards a longer procedural and fluoroscopy times. Thus, the results of the network analysis may have been influenced and should be interpreted with caution. The small study numbers for the comparisons of nMARQ vs. PVAC and nMARQ vs. IRF should be taken into account.

Compared with LBA, CBA has become more promising and increasingly used over the last few years, and in this study, CBA and IRF were comparable concerning procedure and fluoroscopy times. Previous studies have shown that CBA is associated with shorter procedure and fluoroscopy times compared with IRF [57]. However, in this meta-analysis, patients with mixed AF were included, and several trials were randomized with significant heterogeneities. In the sensitive analysis, CBA with CB2 was found to have a significantly shorter procedure time compared with CF-IRF. This result was consistent with the study by Buiatti et al. [58] but was different from that by Jourda et al. [59], which found that the procedural duration was significantly shorter with CF-IRF in comparison with CB2 catheters.

Newly updated and developed technologies, such as CB2 and CF-IRF catheters, should greatly improve the outcomes and shorten the procedural duration. The structural improvements with CB2 could optimize the refrigerant flow and distribution, creating a more uniform freezing zone [60–62].

In addition, the procedure and fluoroscopy times may be shortened even more, as the recently advanced technologies, such as intracardiac echocardiography and high-power short-duration methods, should be utilized for IRF. The newly introduced hot balloon technique is also promising, although the evidence is limited. Thus, the comparison between CBA and IRF needs further investigation; and it is intuitive that differences may become less pronounced, as the efficacy is comparable, especially in centers with a high-volume and more experienced operators.

The results of this study also bring about clinical interests regarding whether the continuous improvement of the CA technologies could help to overcome both the inherent and common limitations, to make the procedure dependent on operator experience and shorten the learning curve for new operators.

5 Limitations

The present study was performed using both pairwise and network meta-analytic methods based on 33 RCTs with 4801 patients; however, there are several limitations.

First, this network meta-analysis intended to evaluate all the CA techniques based on RCTs data; however, some catheters in their first-generation phenotypes, such as nMARQ or PVAC, may not available now and data on their redesigned phenotypes are lacking. Furthermore, as MA and LBA were not commonly used, publication bias may exit, as newer technologies are usually favored over established technologies. Second, the quality of the included studies was adequate, but the blinding of patients and the operators was not possible, and the operator experience varied between the studies. Data were nonuniform in terms of endpoint definitions, follow-up duration, or arrhythmic recurrence monitoring protocols, all of which may cause possible bias, especially in the interpretation of the success rate. In addition, there were considerable heterogeneities, both in the pairwise meta-analysis and between the pairwise and network analyses due to multiple factors. Finally, an assessment of the newest CA technologies, such as hot balloon ablation and high-power ablation, was not available due to the lack of related studies or RCTs until now, and the question for the optimum technique remains open.

6 Conclusions

The efficacy and safety outcomes were comparable among various techniques, and there is insufficient evidence to suggest that one CA technique is superior to another. However, PVAC may be associated with a shorter procedural duration among the included techniques, and CB2 catheters seemed to reduce the procedure time compared with CF-IRF. Further large-scale studies are warranted to compare the available CA techniques and provide an up-to-date recommendation for the superior option.

Authors' contributions XZ and JD designed the research, performed the statistical analysis, and wrote the manuscript text. XX, YL, and ZL performed the literature search and data collation. ML prepared figures and tables. ZW and WM have jointly supervised the work and revised the article critically. All authors read and approved the final manuscript.

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Compliance with ethical standards

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