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REVIEWS

Comparing the efficacy of catheter ablation strategies for persistent atrial fibrillation: a Bayesian analysis of randomized controlled trials

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Abstract

Background Catheter ablation has been recommended as the first-line treatment option for selected patients with atrial fibrillation (AF). However, a widely accepted ablation strategy for persistent AF (perAF) has not yet been established. The benefits of ablation strategies are not conclusive for perAF. There is an urgent need to systematically analyze the results of previous studies and rank these treatment strategies to guide clinical practice.

Methods Randomized controlled trials (RCTs) on ablation for perAF were included. The primary outcome was recurrence of atrial tachyarrhythmia (AT) after a single ablation procedure. A Bayesian random-effects network meta-analysis model was fitted.

Results Twenty-three studies were included in the analysis. A total of 3394 patients and 22 ablation strategies were found in the involved studies. The ablation strategy of pulmonary vein isolation (PVI) + electrical box isolation of the left atrial posterior wall (PBOX) + non-PV trigger ablation (NPV) showed the best treatment effect in terms of the primary outcome. The individualized ablation strategies of mapping and ablation combined with PVI, such as PVI + rotors, PVI + dispersion areas, and PVI + low voltage zone (LVZ) also showed a better ablation effect in perAF.

Conclusions PVI ablation is a widely used strategy in perAF and is recognized as a cornerstone procedure for perAF. The PVI + PBOX + NPV strategy showed the highest rank in our analysis. Mapping and ablation strategies that could provide individualized substrate modification also showed a better rank in our analysis and are believed to be a promising direction for the treatment of perAF.

Keywords Atrial fibrillation · Catheter ablation · Persistent atrial fibrillation · Ablation strategy · Pulmonary vein isolation

1 Introduction

Catheter ablation has been recommended as the first-line treatment option for selected patients with atrial fibrillation (AF). With the development of technology and the deepening of research, it has been demonstrated that pulmonary vein isolation (PVI) by ablation is a well-established treatment strategy in patients with AF [1–3]. However, for persistent AF (perAF), the outcomes with catheter ablation have not yet met the clinical requirements, and a widely accepted ablation strategy in patients with perAF has not been established [3, 4].

Currently, different treatment strategies are used at different treatment centers. In general, three kinds of ablation strategies have been employed in patients with perAF in clinical practice. The first type of strategy is the PVI alone strategy, as used in paroxysmal AF; the second type of strategy is empirical linear ablation, exemplified by tricuspid isthmus linear ablation (CIL), mitral isthmus linear ablation

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(MIL), roof line ablation (RL), and electrical box isolation of the left atrial posterior wall (PBOX), etc., which was derived from the Cox-maze surgery and is used in addition to PVI and. The third strategy is the mapping and ablation strategy, in which the substrate responsible for maintaining fibrillation is first mapped by identifying dynamic phenomena during AF or any abnormal fibrotic area of the atrium (such as complex fractionated atrial electrograms (CFAEs), rotors, dispersion areas, low voltage areas, etc.), then the individualized substrate modification added to PVI is performed [5–7]. However, the benefits of these ablation strategies are not conclusive and results regarding the same ablation strategy from different reports are conflicting. For example, the STAR AF II study showed that the PVI alone had no disadvantage regarding freedom from atrial arrhythmias (AT) or AF compared with an additional ablation strategy beyond PVI (including CFAEs ablation and linear ablation) [8]. Other reports have shown that CFAEs ablation is an effective adjuvant strategy beyond PVI [9]. On the other hand, Kim et al. reported that posterior wall box isolation (PBOX), as an addition to PVI, could improve the rhythm outcome of catheter ablation in a single procedure in patients with perAF, while Lee et al. and Yu et al. reported that PBOX did not influence the rate of recurrent atrial arrhythmia compared to PVI alone [10, 11]. Therefore, there is an urgent need to systematically analyze the results of previous studies and to rank these treatment strategies in order to guide clinical practice.

Recently, there have been fewer head-to-head studies comparing more than three ablation strategies. Several traditional meta-analyses have compared different ablation strategies. However, in those studies, only pairwise comparisons of ablation strategies were performed and the conclusions were not consistent [12–16]. Therefore, we conducted a Bayesian analysis of RCTs to compare the efficacy of different strategies and rank those benefits in perAF patients in order to provide further insight into this matter.

2 Methods

2.1 Search strategy and study selection

This study was approved by Shandong Provincial Hospital Committee of Shandong University. Articles were searched and retrieved from three databases: the Cochrane Central Registered Control System (CENTRAL), PubMed, and Excerpta Medica Database (EMBASE)) until August 23, 2020. The following search terms were used: “persistent atrial fibrillation” AND “ablation” AND “randomized controlled trial.” The specific search strategy in the PubMed database is shown as an example in Table s1 of the supplementary material. After retrieving relevant literature, duplicate documents were first removed, and then we reviewed all titles. The abstracts were next screened according to the related criteria. Finally, we evaluated the qualifications of the related articles adhering to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

2.2 Eligibility criteria

The inclusion criteria for the study were as follows: original data regarding ablation strategy using catheter radiofrequency ablation in patients with perAF, which was defined as perAF that is continuously sustained beyond 7 days [5], published in English, RCT design, first-time ablation, and single procedure. The exclusion criteria were as follows: conference abstracts, lack of data on primary outcome, participants including patients with paroxysmal AF (PAF), each arm containing less than ten participants, reviews, original data regarding hybrid surgery or surgical procedure, and follow-up period less than 6 months. If there were two reports regarding the same research, only the report containing the more complete data was used.

2.3 Data extraction and critical appraisal

Data were extracted from the incorporated articles that passed the initial quality assessment, which included the following: author names, baseline characteristics, number of participants involved in each arm, study design, follow-up duration, procedural details, and interest outcomes. If insufficient information was presented, we attempted to contact the authors to request additional information. The quality of the included studies was assessed using the Cochrane Risk of Bias Tool for RCTs, as previously reported [17]. Any inconsistencies were resolved through discussion.

2.4 Outcome

The primary outcome of our study was the recurrence of any atrial tachyarrhythmia after a single ablation procedure during the follow-up period, which included atrial tachycardia, atrial fibrillation, and atrial flutter. If an adverse event had the potential to result in required hospitalization for more than 24 h, required blood transfusion, or resulted in permanent injury or death, or required an intervention for treatment during the perioperative and follow-up periods, it was considered as a serious adverse event.

2.5 Statistical analysis

A Bayesian random-effects network meta-analysis (NMA) model was used to simultaneously compare multiple regimens. We used Review Manager Version 5.3 to analyze the quality of the involved RCTs. Continuous variables were expressed using weighted mean differences and 95% confidence intervals (CIs), and heterogeneity was assessed using the I^2 statistic. If the values were presented as median and interquartile range, they were converted to mean and standard deviation, as reported previously [18]. As described previously, accounting for the correlation among multi-arm studies, we combined evidence of direct and indirect comparisons of regimens in our NMA model [19]. Evidence consistency was assumed if there was no discrepancy found during the comparison of the direct and indirect evidence [19]. Random effects were allowed in the NMA, and the magnitude of heterogeneity to account for effect heterogeneity across the involved studies was measured. We used Markov chain Monte Carlo (MCMC) algorithms to estimate the OR values of the effects of the twenty two regimens and the associated 95% CIs in the model. We used the gemtc package in R version 3.5.1 (The R Foundation, Vienna, Austria) in our analyses. The setting includes non-informative prior distributions with two parallel chains. During the process, 50,000 samples after a 100,000-sample burn-in were used in every chain. The parameters of the gemtc package were set up according to previous reports [20]. The surface under the cumulative ranking (SUCRA) and rank probabilities were calculated in our analysis to evaluate and rank regimens. Better performance for the outcome was indicated by a larger SUCRA value. Statistical significance was set at $P<0.05$. In order to test the publication bias and small study effects, the funnel plot was performed and the Begg–Mazumdar test and Harbord–Egger test were used [21, 22]. $P<0.05$ indicated the presence of publication bias.

3 Results

3.1 Study selection

A total of 1896 articles were identified through the database search, and one article was added by screen references, as shown in Figure s1. A total of 734 articles were removed as they were duplicates. After title and abstract screening, 155 articles were retained. In the full-text screening process, 16 articles were excluded because they were not RCTs, and 53 were excluded because they lacked interesting outcomes. A further 17 were excluded because they included patients with paroxysmal AF and 26 were excluded because they did not compare different ablation strategies. Six were excluded for other reasons, such as being letters, comments, and reviews. Two were excluded due to non-fixed ablation strategy [23, 24].There were two pairs of reports on the same research [10, 25–27]; only the ones containing the most complete data were included [10, 27]. One study was excluded because it included patients with previous AF ablation [28]. Three studies were excluded because the pre-specified primary outcomes were not reported [5, 29, 30]. Six studies were excluded because the ablation strategies in those studies could not be included in our network of analysis during our pre-analysis [31–36].

Finally, 23 studies were included in our analysis [8, 23, 37–57]. The basic characteristics of the included studies are listed in Table 1. Our study included 3394 patients with perAF. The mean age of all included participants was 58.7 ± 9.9 years, and the percentage of males was 64.9%. There were 22 ablation strategies found in all included studies, including PVI ablation, rotor ablation, CFAE ablation, linear ablation, low voltage zone (LVZ) ablation, non-PV trigger ablation (NPV), and different combinations of the above ablation strategies. The overall percentage of patients being free from any AT after a single ablation procedure in all included studies was 54.6%. The percentage of serious adverse events during the perioperative and follow-up periods was 6.9% (details are shown in Tables 2 in the supplementary information).

The included studies were evaluated using the Cochrane risk of bias tool (shown in Fig. 1). In terms of allocation bias, 13 RCTs were classified as an unclear risk of bias for not detailing the information of random sequence generation [23, 38, 40, 41, 45–50, 52, 55, 56]. In terms of allocation concealment, due to the nature of the ablation procedures, it was believed that the blinding measure would not affect outcomes. Thus, performance and detection biases entailed a low risk in all included RCTs. Seven of the included studies were noted as having an unclear risk in terms of attrition bias because the dropout rates of those studies were between 2 and 20% [8, 42, 45, 50, 53, 54, 57]. The pre-specified primary outcome was found in all involved studies, but in 13 studies, one or two pre-specified interest outcomes were not reported, which were considered to have an unclear risk in terms of reporting bias [23, 40–42, 44–48, 51, 54, 55, 57]. Regarding other potential biases, six studies had an unclear risk due to small simple size [23, 38, 42, 43, 54, 55], while the others were judged as having low risk. For the publication bias, Begg's test gave a value of $Pr>|z|=-0.79$, Egger's test gave a value of $p>|t|=0.3573$, and funnel plot is shown in Figure s4, all of which suggested no significant publication bias for the included studies.

3.2 Primary outcome

There were 23 studies and 22 ablation strategies involved in the analysis of primary outcomes [8, 23, 37–57]. The network of the primary outcome is shown in Fig. 2. Twenty-two ablation strategy regimens were compared in our analysis, which included: ganglionated plexus ablation (GP), PVI, PVI + tricuspid isthmus linear ablation (CIL), PVI + CIL + mitral Isthmus linear ablation (MIL) + linear ablation of left

Table 1 Basic characteristics of involved studies

Study	Design	Involved patients	Comparison	Ages (years)	Males (%)	Follow-up duration (months)
1. 2006 Willems et al	RCT	Long-standing persistent AF	PVI + CIL vs PVI + CIL + MIL + RL	58.6 ± 9.0	NA	16.0 ± 3.3
2. 2008 Oral et al	RCT	Long-standing persistent AF	PVI vs PVI + CFAEs	59.9 ± 9.3	82.00%	10.0 ± 3.0
3. 2010 Mikhaylov et al	RCT	Long-standing persistent AF	PVI + MIL + RL vs PVI + MIL + RL + SL	50.6 ± 9.9	64.70%	20.3 ± 3.9
4. 2013 Pokushalov et al	RCT	Persistent AF; long-standing persistent AF	PVI + CIL + GP vs PVI + CIL + MIL + RL	54.5 ± 6.5	78%	12.0 ± 0.0
5. 2013 Wang et al	RCT	Long-standing persistent AF	PVI + MIL + RL + CFAEs vs PVI + CIL + MIL + RL + CFAEs vs PVI + CFAEs	63.0 ± 9.0	62.7%	32.0 ± 9.0
6. 2014 Mamchur et al	RCT	Persistent AF	GP vs PVI vs PVI + GP	56.2 ± 8.8	60%	16.0 ± 0.0
7. 2014 Wang et al	RCT	Long-standing persistent AF	PVI + LVZ vs stepwise	62.5 ± 8.5	61.30%	7.8 ± 3.4
8. 2014 Atienza et al	RCT	Persistent AF	PVI vs PVI + driver(HFSA)	54.5 ± 9.5	81.20%	12.0 ± 0.0
9. 2015 Dong et al	RCT	Persistent AF	PVI + CIL + MIL + RL vs stepwise	55.0 ± 11.0	76%	12.0 ± 0.0
10. 2015 Verma et al	RCT	Persistent AF	PVI vs PVI + CFAEs vs PVI + MIL + RL	60.2 ± 9.1	78.30%	18.0 ± 0.0
11. 2015 Vogler et al	RCT	Persistent AF	PVI vs. stepwise	61.7 ± 10.2	62.70%	12.0 ± 0.0
12. 2015 Wong et al	RCT	Persistent AF; long-standing persistent AF	PVI + MIL + RL vs PVI + MIL + RL + CFAEs	61.0 ± 10.0	75%	35 ± 5
13. 2015 Zhang et al	RCT	Persistent AF	PVI + MIL + RL vs PVI + RL + AL	58.1 ± 13.1	56%	31.8 ± 9.4
14. 2016 Lin et al	RCT	Persistent AF	PVI + rotor vs PVI + CFAEs	55.0 ± 9.0	77.90%	17.7 ± 8.17
15. 2017 Ammar-Busch et al	RCT	Persistent AF	PVI + CFAEs vs PVI + RL + AL + CFAEs	64.0 ± 9.0	79%	12.0 ± 0.0
16. 2017 Fink et al	RCT	Persistent AF; long-standing persistent AF	PVI vs PVI + CFAEs	61.5 ± 9.7	71%	12.0 ± 1.25
17. 2017 Kim et al	RCT	Long-standing persistent AF	PVI + CIL + PBOX + AL vs. PVI + CIL + PBOX + AL + CFAEs	61.6 ± 10.9	71.40%	22.3 ± 13.2
18. 2017 Yu et al	RCT	Patients with persistent AF changing to paroxysmal AF	PVI + CIL vs PVI + CIL + PBOX + AL	60.4 ± 10.1	75%	18.6 ± 11.4

Table 1 (continued)

Study	Design	Involved patients	Comparison	Ages (years)	Males (%)	Follow-up duration (months)
19. 2017 Yang et al	RCT	Persistent AF	PVI + CIL + LVZ vs stepwise	57.4 ± 9.0	77.20%	18.0 ± 0.0
20. 2018 Mohanty et al	RCT	Persistent AF; long-standing persistent AF	PVI + rotor vs PVI + PBOX + NPV	66.2 ± 9.1	72.40%	11.9 ± 8.8
21. 2019 Lin et al	RCT	Persistent AF	PVI + dispersion vs stepwise	63.2 ± 9.8	62.00%	6.7 ± 2.2
22. 2019 Yamaji et al	RCT	Persistent AF	PVI + RL vs PVI + RL + AL	68.0 ± 10.0	77.50%	25.3 ± 4.0
23. 2020 Yao et al	RCT	Persistent AF	PVI + RL vs PVI + RL + AL	57.3 ± 10.1	81.80%	24.0 ± 0.0

RCT randomized controlled study, *AF* atrial fibrillation, *PVI* pulmonary vein isolation ablation, *CIL* tricuspid isthmus linear ablation, *MIL* mitral isthmus linear ablation, *SV* superior vena cava vein isolation ablation, *SL* linear ablation of left atrial septal wall, *PL* linear ablation of left atrial posterior wall, *RL* linear ablation of left atrial roof, *CFAEs* complex fractionated atrial electrograms ablation, *NPV* non-PV trigger ablation, *GP* ganglionated plexus ablation, *AL* anterior wall linear ablation, *LVZ* low voltage zone ablation, *PBOX* electrical box isolation of left atrial posterior wall, *NA* not available

atrial roof (RL), PVI + CIL + MIL + RL + CFAEs, PVI + CIL + electrical box isolation of left atrial posterior wall (PBOX) + linear ablation of left atrial anterior wall (AL), PVI + CIL + PBOX + AL + CFAEs, PVI + CIL + GP, PVI + CIL + low voltage zone ablation (LVZ), PVI + MIL + RL, PVI + MIL + RL + linear ablation of left atrial septal wall (SL), PVI + MIL + RL + CA, PVI + rotors, PVI + CFAEs, PVI + dispersion areas, PVI + PBOX + NPV, PVI + GP, PVI + LVZ, PVI + RL, and PVI + RL + AL, PVI + RL + AL + CFAEs, stepwise. We assumed that all ablation strategies had comparable efficacies in regards to the primary outcome. We set PVI as the reference strategy because it is the cornerstone of catheter ablation in patients with AF.

As shown in Fig. 3, compared to an ablation strategy with PVI alone, most of the additional substrate ablation strategies did not show additional benefit of primary outcome, except for the ablation strategies PVI + CIL + PBOX + AL, PVI + CIL + PBOX + AL + CFAEs, and PVI + CIL, which were shown to be less free from any atrial tachyarrhythmia occurrence after ablation in patients with perAF. Pairwise comparisons among the regimens are shown in Supplementary Figure s2.

Table 2 displays SUCRA values for the primary outcome illustrates the performance of the tested regimens. It was showed that the regimen PVI + PBOX + NPV got the highest SUCRA value regarding the primary outcome. The regimens of ablation strategies that included PVI + dispersion areas (PVI + LVZ, PVI + GP, PVI + rotors, PVI + CIL + GP, and PVI + CIL + LVZ) also showed better ranking of treatment effects compared to the PVI alone strategy. It is worth pointing out that ablation strategies using additional empirical linear ablation as a complement to PVI, such as PVI + MIL + RL + CFAE, PVI + CIL + MIL + RL, PVI + MIL + RL, PVI + RL, PVI + MIL + RL + SL, PVI + RL + AL, stepwise, PVI + RL + AL + CFAEs, and PVI + CIL, showed poor ranking of treatment effect regarding the primary outcome. Most notably, it was shown that the most aggressive empirical linear ablation strategies, such as PVI + CIL + PBOX + AL and PVI + CIL + PBOX + AL + CFAEs, achieved the worst ranking of treatment effect in terms of the occurrence of freedom from any AT after ablation. In order to examine the long-term effect of each ablation strategies, a subgroup analysis of RCTs with follow-up period more than 1 year was performed. Twenty RCTs and twenty-one ablation strategies were included. The result of ranking is shown in Table s3, which was similar to the result of primary outcome.

The result of the model diagnostics of the NMA under the assumption of evidence consistency is shown in Figure s3 in the supplementary material. It was found that the Gelman-Rubin statistics were close to 1 fast, and MCMC chains converged well in trace plots, which demonstrated that the MCMC chains were well mixed. Figure 4 shows the result of statistical evidence inconsistency using the node-splitting approach. Seven comparisons estimated both direct and indirect comparisons. There were no statistically significant differences between direct and indirect comparisons.

Table 2 SUCRA of primary outcome

	Ablation strategy	The value of SUCRA
1st	PVI + PBOX + NPV	0.902585
2nd	PVI + dispersion areas	0.886794
3rd	PVI + LVZ	0.752546
4th	PVI + GP	0.7303
5th	PVI + rotors	0.675116
6th	PVI + CIL + GP	0.663429
7th	PVI + CIL + MIL + RL + CFAEs	0.626616
8th	PVI + CIL + LVZ	0.613157
9th	PVI	0.571165
10th	PVI + CIL + MIL + RL	0.567336
11th	PVI + MIL + RL + CFAEs	0.563937
12th	PVI + MIL + RL	0.498058
13th	PVI + RL	0.474289
14th	PVI + CFAEs	0.46074
15th	stepwise	0.444728
16th	PVI + MIL + RL + SL	0.436136
17th	PVI + RL + AL	0.424349
18th	GP	0.305047
19th	PVI + RL + AL + CFAEs	0.187823
20th	PVI + CIL	0.118869
21st	PVI + CIL + PBOX + AL	0.07316
22nd	PVI + CIL + PBOX + AL + CFAEs	0.02382

PVI pulmonary vein isolation ablation, *CIL* tricuspid isthmus linear ablation, *MIL* mitral Isthmus linear ablation, *SL* linear ablation of left atrial septal wall, *RL* linear ablation of left atrial roof, *CFAEs* complex fractionated atrial electrograms ablation, *NPV* non-PV trigger ablation, *GP* ganglionated plexus ablation, *AL* anterior wall linear ablation, *LVZ* low voltage zone ablation, *PBOX* electrical box isolation of left atrial posterior wall, *SUCRA* the surface under the cumulative ranking

We used DIC to compare the model fit of the NMA models with and without the assumption of evidence inconsistency in our analysis. The results showed that the two models provided similar DIC values (DIC 97.17, $I^2 = 3\%$ vs. DIC 97.30, $I^2 = 9\%$), showing good consistency.

4 Discussion

There were 22 ablation strategies found within all included studies, most of which included PVI. The overall percentage of the occurrence of freedom from any AT after a single ablation procedure in all included studies in our study was 54.6%. According to the results of rank regimens, the ablation strategy of PVI + PBOX + NPV showed the best treatment effect regarding the occurrence of freedom from any AT after a single ablation procedure in patients with perAF. The individualized ablation strategies that pertain mapping first and then ablating combined with PVI, such as PVI + rotors, PVI + dispersion areas, and PVI + LVZ, also showed a better ablation effect.

4.1 PVI ablation strategy

Currently, around the world, different centers have different ablation procedures during the process of ablation in patients with perAF, and there are too many different types of ablation procedures for treating perAF. In the course of our research, we found 33 different combinations of ablation strategies and the common point of these ablation strategies was that most of them were based on PVI. For example, among the 22 ablation strategies included in our analysis, only one did not include PVI ablation, and it showed less benefit in terms of occurrence of freedom from any AT after a single ablation procedure. It seems that PVI as an ablation strategy is not only recognized as the cornerstone of radiofrequency ablation of paroxysmal AF but is also widely recognized and accepted during radiofrequency ablation of perAF. However, the success rate of PVI alone to prevent the recurrence of AF in patients with perAF was reported to be between 15 and 40%, which is much lower than that reported in patients with paroxysmal AF [3]. During our analysis, consistent with previous reports, it was found that the percentage of the occurrence of freedom from AT after single procedure of PVI alone ablation ranged from 54 to 63.9% (54% ± 9.9%). The limited effect of PVI ablation alone in perAF may be due to the nature of the ablation strategy, which was based on the theory that PVs are the most frequent trigger source of AF [58]. It was reported that the role of PV activity as a driver of AF decreased with left atrial dilatation and time in AF [59], and those patients with persistent, longstanding persistent and permanent AF had a lower proportion of "active PVs" compared to patients with paroxysmal AF [59]. Therefore, it seems that simply isolating PVs is not sufficient in patients with perAF. However, there was an argument that PVI alone should be the first approach to peAF and that additional ablation should not be performed in the first ablation procedure in patients with peAF [7]. Especially after STAR AF II was published and showed that PVI alone had no disadvantage in freedom from AT or AF compared with additional ablation strategies beyond PVI [8]. This finding was not supported by our results. In our ranking analysis results, it was found that the therapeutic effect of PVI alone was ranked in the middle of all treatment strategies, with several additional ablation strategies in combination with PVI showed better outcomes. This demonstrated that the PVI alone strategy was not good enough for patients with perAF and that a better outcome regarding freedom from ATs after a single ablation procedure could be achieved. Therefore, in our opinion, in patients with perAF, additional ablations

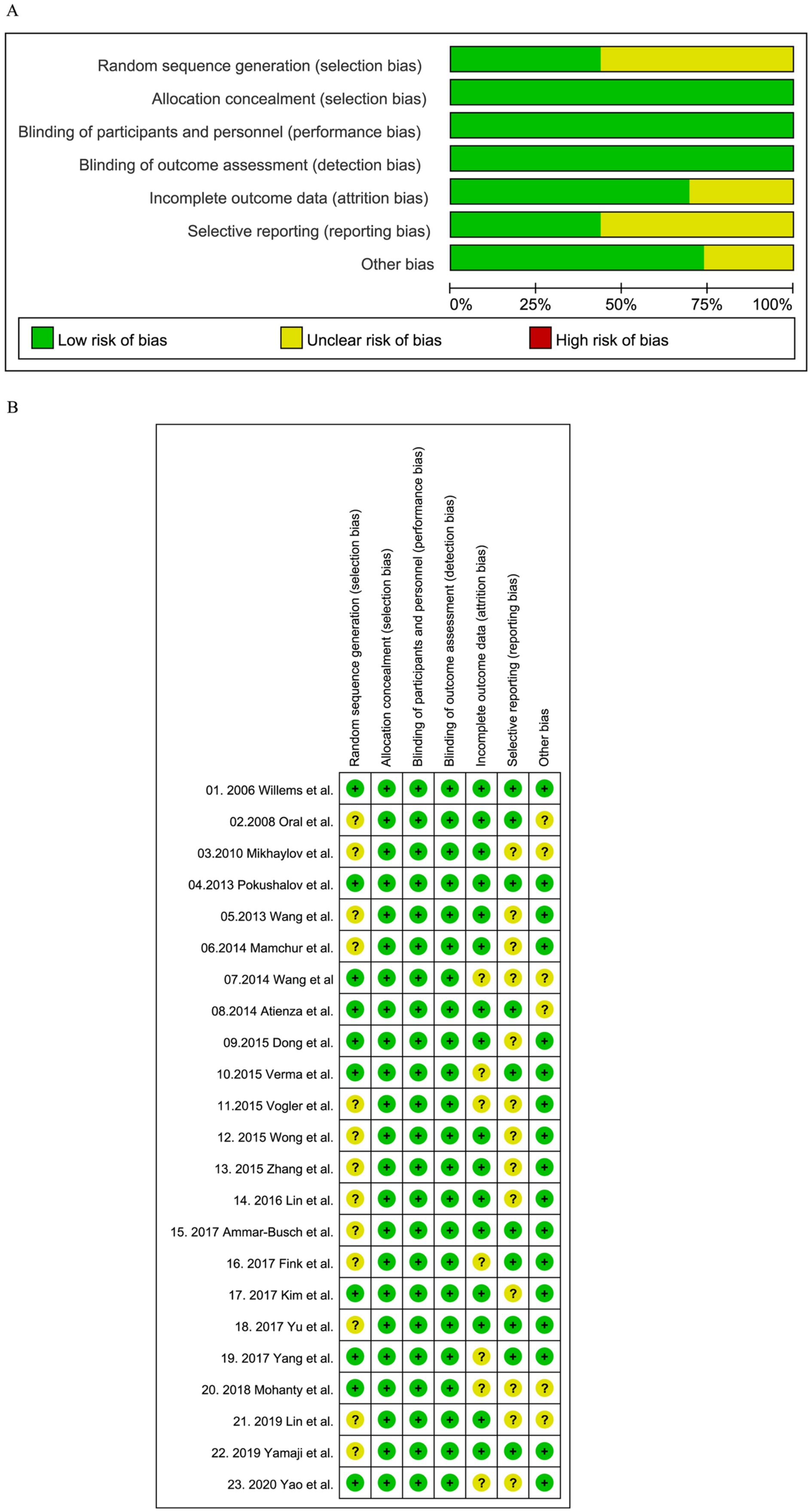

Fig. 1 Risk of bias summary. **A** Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies. **B** Risk of bias summary: review authors' judgements about each risk of bias item for each included study

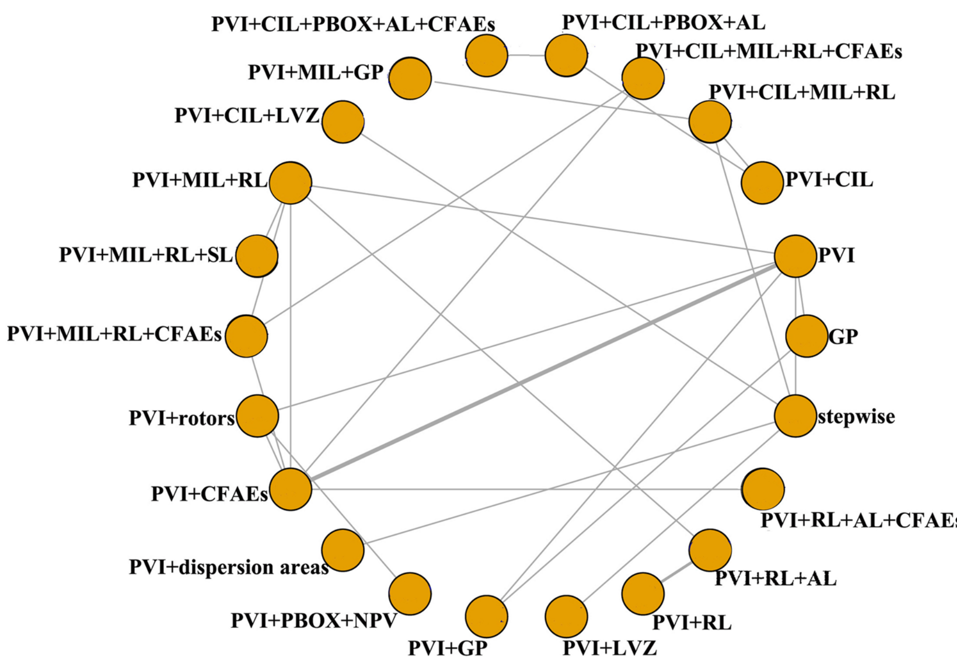

Fig. 2 Network of 22 ablation strategy regimens. PVI pulmonary vein isolation ablation, CIL tricuspid isthmus linear ablation, MIL mitral Isthmus linear ablation, SL linear ablation of left atrial septal wall, RL linear ablation of left atrial roof, CFAEs complex fractionated atrial electrograms ablation, NPV non-PV trigger ablation, GP ganglionated plexus ablation, AL anterior wall linear ablation, LVZ low voltage zone ablation, PBOX electrical box isolation of left atrial posterior wall

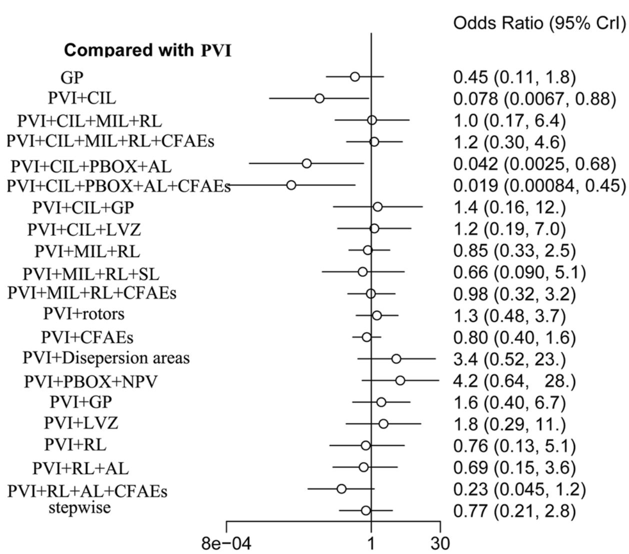

Fig. 3 Forest plots for primary outcome, PVI pulmonary vein isolation ablation, CIL tricuspid isthmus linear ablation, MIL mitral Isthmus linear ablation, SL linear ablation of left atrial septal wall, RL linear ablation of left atrial roof, CFAEs complex fractionated atrial electrograms ablation, NPV non-PV trigger ablation, GP ganglionated plexus ablation, AL anterior wall linear ablation, LVZ low voltage zone ablation, PBOX electrical box isolation of left atrial posterior wall

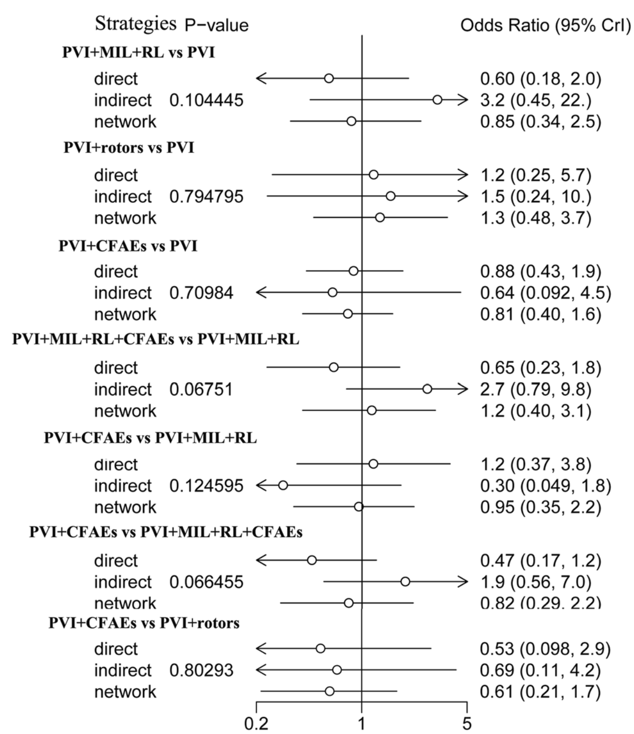

Fig. 4 The result of statistical evidence inconsistency of primary outcome by node-splitting approach. There were no statistically significant differences for the primary outcome. PVI pulmonary vein isolation ablation, CIL tricuspid isthmus linear ablation, MIL mitral isthmus linear ablation, SL linear ablation of left atrial septal wall, RL linear ablation of left atrial roof, CFAEs complex fractionated atrial electrograms ablation, NPV non-PV trigger ablation, GP ganglionated plexus ablation, AL anterior wall linear ablation, LVZ low voltage zone ablation, PBOX electrical box isolation of left atrial posterior wall

targeting the substrate maintaining fibrillation should be developed in order to improve outcomes. In our discussion, we classified these additional ablation strategies into two types: empirical linear ablation strategy and mapping and ablation strategy.

4.2 Empirical linear ablation

The linear ablation approach is rooted in the Cox maze surgical approach. During the conduction of the Cox maze surgery, the posterior wall of the left atrium and PVs are isolated and additional linear scar creation in the left and right atria is performed. The proportion of patients with sinus rhythm could achieve up to 84% in perAF after a 7-year follow-up period [60]. To simulate the effect of Cox maze surgery, most studies included in our research utilized different linear ablations or different combinations of linear ablation. Among these, the most commonly used ablation lines were CIL, MIL, and RL. Unfortunately, it was found that most of the linear ablation or their combination strategies additional to PVI were not better than PVI alone in preventing the recurrence of atrial tachyarrhythmia during the ranking analysis in our research, which was consistent with the results of previous RCTs [8, 57, 61]. It was assumed that the reason for this lack of benefit associated with additional linear ablation or their combination strategies may be that the two main purposes of those strategies, which were creating endocardial line blocks to emulate the Cox maze process and eliminating arrhythmogenetic atrial substrates, were not achieved [62]. It has been demonstrated that complete transmural lesions are difficult to achieve with a single ablation procedure, which leads to incomplete linear block [8, 63]. On the other hand, linear ablation may destroy normal myocardial tissue and disrupt the connection of different atrial areas, which would lead to new, iatrogenic areas of arrhythmogenesis [57, 63, 64]. Based on the above reasons, doubts about whether linear ablation should be performed have been raised and some investigators have suggested that lines may not be the correct supplemental targets for ablation [65, 66].

Fortunately, a PBOX ablation strategy may be employed, including PVI + MIL + RL + linear ablation of the bottom of the left atrium in order to isolate the posterior wall of the left atrium, which showed great treatment benefit of sinus rhythm maintenance in patients with perAF after a single ablation procedure. In the ranking analysis of our research, it was found that the ablation strategy of PVI + PBOX + NPV showed the best potential in preventing the recurrence of AT. This result is consistent with a recently published observational study and a previous meta-analysis [15, 67], in which PBOX, in addition to PVI, was significantly associated with fewer episodes of recurrent perAF in patients with perAF. The reason for the treatment effect on PerAF of the PBOX ablation strategy differing from other linear ablation strategies may be due to embryonic histological causes. PVs and the left atrium posterior wall (LAPW) all originate from a single embryonic PV during development of the human heart, which provides the anatomic basis for the noted unstable electrophysiological characteristics, suggesting that these two structures may be involved in the development of AF [68, 69]. It was also reported that LAPW was also believed to be the main site targeted by fibrosis and lymphatic mononuclear infiltration in the atrium during the development of perAF [70]. Thus, the PBOX ablation strategy, which was the ablation strategy most closest to the surgical Cox maze procedure, may isolate the triggers and rotors in the LAPW that could initiate or drive fibrillatory activities in the atrium and decrease the percentage of recurrence of AT [71]. Meanwhile, it is worth pointing out that the most aggressive empirical ablation strategy among those involved in our analysis, which included AL ablation using PVI + PBOX, showed the worst effect for preventing recurrence of AT. The original intention of adding an AL line was to imitate the "Dallas line" in the Cox maze procedure. However, due to the distance of the AL and difficulties in transmural ablation, newer and iatrogenic areas of arrhythogenesis in the atrium would occur during the ablation process. This is probably because of the above reasons. This ablation strategy did not show better ablation benefits and even became the ablation strategy with the worst potential in preventing the recurrence of atrial tachyarrhythmia after a single ablation procedure.

On the other hand, the effect of PVI + PBOX + NPV ablation strategy may also benefit from the participation of the NPV ablation strategy. Previous studies have demonstrated that elimination of non-PV triggers was associated with improved arrhythmia-free survival in perAF patients [72]. Takamiya et al. [73] also reported that although PVI + PBOX alone could achieved good clinical outcomes in perAF, additional NPV ablation may improve the outcome after multiple procedures. However, due to the nature of meta-analysis, we could not distinguish the effect of PVI + PBOX with or without NPV ablation strategy. Further researches are needed.

Notably, during our analysis, the stepwise ablation strategy, a highly promising ablation strategy, did not show a better potential for preventing recurrence of AT compared to PVI + PBOX + NPV and other ablation strategies, such as PVI + LVZ, PVI + rotors, and PVI + dispersion areas, after a single ablation procedure, but only showed a mediocre therapeutic effect in our ranking analysis results. The biggest feature of this ablation strategy is to gradually advance ablation of atrial fibrillation until termination, involving various linear ablation strategies (MIL, RL, CIL, CFAEs, etc.). A meta-analysis by Li et al. in 2019 clearly demonstrated that AF termination did not have a reliable procedural endpoint during the ablation of perAF [16]. Previous studies have shown similar results [53, 61]. Therefore, it is understandable that a stepwise ablation strategy that terminates atrial fibrillation as the ablation endpoint did not achieve outstanding performance in patients with perAF.

Therefore, combining the results of previous studies and our analysis, it is shown that the ablation strategy of additional PBOX + NPV to PVI had the best treatment potential in preventing the recurrence of AT among all empirical linear ablation strategies in patients with perAF, which should be recommended in patients with perAF among all empirical linear ablation strategies.

5 Mapping and ablation strategies

There were 4 mappings first, followed by ablation strategies CFAEs, LVZ, rotors, and dispersion areas) in addition to PVI, observed in our research. All of these mapping and ablation strategies were aimed at targeting the atrial substrate responsible for AF maintenance to perform individualized substrate modification in addition to PVI in patients with perAF. Theoretically, atrial substrate would be heterogeneous in a persistent population, for AF duration, cardiac function, heart commodities, and left atrial diameter might differ markedly in patients with perAF. Therefore, the assumption that individualized mapping and ablation would create additive benefits is plausible [7]. The main question lies in determining the correct mapping and ablation target in patients with AF. In general, mapping and ablating of dynamic phenomena during AF and fibrotic substrates are the two main directions employed in current clinical practice [6], the first of which includes CFAEs, rotors, etc., and the other includes dispersion area mapping, LVZ mapping, etc. According to our analysis, most of the ablation strategies based on the above mapping technologies had better rankings. This demonstrates that mapping and ablation strategies added to PVI may be a promising direction for treating PerAF. The only drawback is that the studies that evaluated these strategies were all small RCTs. Large RCTs are needed. The PLEA trial, a prospective, randomized, multicenter trial (NCT04216667), would provide more support.

It should be pointed out that, unlike the performance of most other 3 mapping and ablation strategies involved in our analysis, the CFAE ablation strategy did not have additional benefits beyond PVI in our analysis. The CFAE ablation strategy was the first electrogram-based ablation and fully evaluated strategy in previous studies and was a frequency used strategy in addition to PVI in patients with perAF in our study [8, 31, 32, 38, 40, 49, 50]. Some previous studies reported that CFAE ablation did not yield additive benefits when performed in addition to PVI [74]. Our ranking and pairwise analysis results were consistent with previous research. Jadidi et al. [75] reported that CFAEs represent a collision of wavefronts during AF, and sites with CFAEs during AF correspond in most cases to normal electrograms during sinus rhythm, which highlights the functional and passive nature of CFAEs. Above all, it seems that CFAEs may not be an ideal target for ablation, and we do not encourage operators to perform CFAEs in patients with perAF.

6 Limitations

The process of this study was strictly carried out according to the priority report items of the network meta-analysis. Although the evidence network has good homogeneity and no inconsistent evidence is seen, the research itself and the included RCTs still have certain limitations, which may affect the strength of the argument. This was mainly manifested in the following: first, the methodological quality of some included RCTs was generally not high and multiple items of the risk of bias assessment were unclear. Some studies did not report the specific method of random sequence generation and some did not report secondary outcomes, which could cause additional bias in our analysis. Second, consistent comparisons between studies may be precluded; for heterogeneous populations (such as persistent AF, long-standing persistent AF, persistent + long-standing persistent AF, etc.) recruited in the included studies and the ablation target and electrophysiological endpoint of the ablation strategies differ substantially in different RCTs. Third, not all ablation strategies used in patients with perAF were included in our research, as some of them could not be included in the network of analysis in our pre-test. Especially, it could not distinguish the effect of PVI + PBOX with or without NPV ablation strategy. Even so, we could get some clues regarding treatment effects by analyzing strategies similar to them. Future studies are needed to address the specific effects of these strategies in patients with perAF. Fourth, some of the ablation strategies in our study were only employed in one or two centers and in small-scale RCTs, especially for mapping and ablation strategies such as PVI + LVZ, PVI + dispersion areas, and PVI + rotors. Therefore, our study merely pointed out the direction of future attention in clinical practice. Large-scale, multicenter RCTs are needed. Perhaps the ongoing PLEA trial might provide more information. Fifth, although we obtained a clear ranking result by analyzing, only seven loops contained both direct and indirect comparisons, and only some pairwise comparisons between involving strategies showed statistically significant differences. A possible reason for this is that the sample size was not large enough, and there was not enough power to detect statistical differences. As more research results are published, this problem may be solved.

7 Conclusion

Above all, no ablation strategy has been found that could defeat the enemy in one move in patients with perAF until now. Thus far, it has been demonstrated that PVI ablation is a widely used strategy in PerAF and is recognized as a cornerstone procedure not only for primary AF, but also for perAF. Among the empirical ablation strategies, the PVI + PBOX + NPV strategy showed the best rank in our analysis. Mapping and ablating strategies that could provide individualized substrate modification, such as rotors, LVZ, and dispersion area ablation in addition to PVI also showed a better rank in our analysis and are believed to be promising directions for the treatment of perAF, except for CFAEs. It is believed that further large-scale multicenter RCTs are needed.

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Declarations

Conflict of interest The authors declare no competing interests.

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