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Effectiveness and safety of different types of ablation modalities in patients with atrial fibrillation: a bayesian network meta-analysis from randomized controlled trials

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Abstract

Introduction Atrial fibrillation (AF) is the most common cardiac arrhythmia, which significantly contributes to morbidity, mortality, and a diminished quality of life. Despite advancements in pharmacological treatments, many AF patients do not achieve adequate symptom control with oral medications. This network meta-analysis seeks to provide comprehensive evidence to guide clinical decision-making and optimize ablation strategies for patients with atrial fibrillation.

Methods This network meta-analysis (NMA) was conducted in accordance to PRISMA NMA Checklist of Items (PROSPERO No. CRD42024577782). A comprehensive search was performed across major literature databases (PubMed, Scopus, CENTRAL, ProQuest, and Web of Science) up to July 10, 2024. Data analyses were performed using Rstudio v.4.4.1 employing Bayesian NMA with random-effects models. Sensitivity, subgroup, and network meta-regression analyses were also conducted. SUCRA values were estimated to present the ranking of each treatment in the network. Meta-proportions with GLMM (Generalized Linear Mixed Model) also performed to analyze the safety outcomes.

Results A total of 6332 AF patients from 46 randomized controlled trials (RCTs) were included. NMA demonstrate epicardial (surgical) approach, especially video-assisted thoracoscopic surgery (VATS) (OR 1.54; 95%CrI [1.03,2.38]; SUCRA 89.61) exhibited superiority to reduce the AF recurrence in AF patients. Hybrid epicardial-endocardial ablation (OR 1.51; 95% CrI [0.82,2.82]; SUCRA 85.7) had a similar freedom from AF rate to VATS. Subgroup and network meta-regression analysis revealed that AF type ((β -0.415; [-0.776;-0.042]) and AF duration (β 0.602; [0.066;1.079]) influence the freedom from AF rate. Meta-proportion indicated that surgical or hybrid ablation exhibited a higher risk of mortality (Prop = 5.07%), pericardial effusion (Prop = 4.35%), and phrenic nerve injury (Prop = 4.35%).

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Conclusion NMA demonstrated higher effectiveness of VATS and hybrid ablation in reducing the recurrence rate of AF. Despite complications associated with surgical and hybrid approaches have higher prevalence, type of complications encountered in this approaches are less diverse.

Keywords Atrial fibrillation, Catheter ablation, Surgical ablation

Background

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting millions worldwide and significantly increasing the risk of stroke and heart failure [1]. The global prevalence of AF has been steadily rising, with an estimated 59.7 million cases in 2019, nearly double the number in 1990 [2]. AF significantly contributes to morbidity, mortality, and a diminished quality of life. Despite advancements in pharmacological treatments, many patients with persistent or paroxysmal AF do not achieve adequate symptom control with medications alone [3]. Consequently, definitive treatments such as surgical or catheter ablation are often necessary.

Catheter ablation (CA) has become a widely performed procedure for AF, emerging as a viable treatment following Haissaguerre et al.'s (1998) [4] discovery of ectopic foci in the pulmonary veins as triggers for AF. Since then, CA techniques have evolved to include radiofrequency ablation, which uses heat to create lesions that block abnormal electrical pathways, and cryoballoon ablation, which uses cold temperatures for the same purpose [5, 6]. Advances in AF ablation tools and techniques, including laser, ultrasound, and other balloon ablation technologies, are ongoing, though results are still limited [7].

Surgical ablation (SA) is primarily performed concomitantly with other surgical procedures but can be a first option for patients with persistent AF after the failure of antiarrhythmic drug therapy [7]. Surgical procedures often involve more extensive lesion sets compared to CA, potentially offering better outcomes for certain patient populations. The development of new ablation technologies, including bipolar radiofrequency energy clamp, has renewed interest in surgical procedures [8]. Less invasive surgical techniques, such as video-assisted thoracoscopic surgery (VATS), have shown promise, with studies reporting benefits in modifying the arrhythmogenic substrate [9, 10].

Studies have shown varying outcomes for different catheter and surgical ablation modalities. Definitive recommendations await more data, particularly in comparing outcomes of various surgical and catheter-based ablation techniques. This study aims to conduct a systematic review and network-meta-analysis of randomized controlled trials to compare the outcomes of different ablation modalities in patients with AF. By synthesizing data from multiple studies, this analysis seeks to provide comprehensive evidence to guide clinical decision-making and optimize treatment strategies for patients with AF.

Methods

This study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Network Meta-Analysis Checklist of Items (Table S1) [11]. Our study protocol has been registered on PROSPERO (CRD42024577782).

Search strategies

A comprehensive systematic search was performed across major literature databases (PubMed, Scopus, CENTRAL, ProQuest, and Web of Science) up to July 10, 2024. We developed a list of primary keywords, including "atrial fibrillation", "catheter ablation", and "surgical ablation" to ensure comprehensive coverage in the search results. Subsequently, we added several Medical Subject Headings (MeSH) and other accessible terms to construct the database-specific search terms. The full search terms for each database are provided in Table S2.

Study selection

The initial search results from each database were exported and organized using Google Sheets (Google LLC, Mountain View, CA, USA). Following that, we removing duplicate studies, and the remaining records were screened based on the studies title and abstract. Subsequently, we investigate the availability of the published full texts of the remaining studies, and all remaining studies were thoroughly judged according to the pre-specified eligibility criteria. The reasons for exclusion from each screening step were reported in the spreadsheet as appropriate and presented in PRISMA flow diagram. The literature database search and study selection process were performed by five investigators independently (FMA, VV, BSW, APW, JOH). Any discrepancies were resolved by group discussion.

Eligibility criteria

The Population, Intervention, Comparison, Outcome (PICO) framework was adapted to designed specific eligibility criteria (Table 1) [12]. The pre-specified eligibility criteria can be accessed in Supplementary Methods.

Data extraction

Pre-specified checklist for data extraction process were developed and tabulated within the spreadsheet by FMA.

Table 1 PICO framework

Components of PICO	Definition
Population	Patients with atrial fibrillation
Intervention	- High power short duration (HPSD) radiofrequency - Very high power short duration (vHPSD) radiofrequency - Cryoballoon - Laser balloon - Microwave - Minimally invasive thoracoscopic epicardial pulmonary vein isolation (MIPI) - Video-assisted thoracoscopic surgery (VATS) - Hybrid
Comparison	Low power long duration (LPLD) radiofrequency
Outcome	- Primary Outcome (Effectiveness): Freedom from AF - Secondary Outcome (Safety): Every complication that occur with ablation

PICO, Population, Intervention, Comparison, Outcome; LPLD, low power long duration; HPSD, high power short duration; vHPSD, very high power short duration; MIPI, minimally invasive thoracoscopic epicardial pulmonary vein isolation; VATS, video-assisted thoracoscopic surgery

Four investigators, consisting of VV, BSW, APW, and JOH performed the extraction process and checked the collected data for their eligibility, and any disagreements were promptly resolved. The data extracted include the trial name (RCT that does not have trial name will be extracted using name of the first author and year of publication), the eligibility criteria of each included studies, ablation methods, modalities, device, and ablation line/set used from each study, trial identifier, study location, patient characteristics, age of participants at baseline, participants dropped-out in intervention group, adherence rate, proportion of female, type of analysis, sample size, duration and power for radiofrequency modality, type of catheter (contact force [CF]-sensing or non CF-sensing), blanking time, rhythm assessment tool, length of follow-up, procedure (left atrial or bi-atrial), duration of AF, left atrial (LA size), hypertension proportion, and procedure time. Data with sufficient coverage were included and presented in a tabular format with qualitative characteristics and outcomes.

Quality assessment of individual studies

Five investigators (FMA, VV, BSW, APW, and JOH) independently performed a methodological quality assessment to evaluate the quality assessment and risk of bias of each eligible study using the Cochrane Collaborations' Risk of Bias 2 (RoB-2) tool [13]. Any disagreements of judgements were resolved by a group discussion. The RoB-2 plots were generated using the 'robvis' tool [14].

Statistical analysis

Network meta-analysis were performed using gemtc [15] packages in Rstudio version 4.4.1 (Posit, Boston, MA, USA) and MetaInsight v 6.0.1 [16]. The effect sizes were estimated using Bayesian network meta-analyses consistency models with Markov Chain Monte Carlo (MCMC) simulation in random-effects model. Binomial likelihood with a logistic regression function was used to estimate OR. For the main analysis, we used a uniform prior distribution model and produced four chains of 10,000 samples (100000 Markov Chain Monte Carlo simulation, keeping every 10th iteration) after discarding the first 5000th iterations for Bayesian network meta-analysis. We confirmed that the number of interactions was sufficient for convergence through trace and density plot (Table S3) and Potential Scale Reduction Factor (PSRF) in Gelman-Rubin-Brooks plot (Figure S1). The model fit of each MCMC simulation also assessed through Deviance information criterion (*DIC*), which is obtained through $D_{bar} + {}_{p}D$ value. Publication bias was assessed both qualitatively using an inverted funnel plot and quantitatively using Egger's regression test, where $p < 0.05$ considered as significant small study effects [17]. Within-comparison between-trial heterogeneity was examined with I^2 statistics [18]. The inconsistency assessment was conducted using the Separating Indirect from Direct Evidence (SIDE) method with node-split command [19]. Global inconsistency was assessed used Deviance Information Criterion (*DIC*) of consistency models [20, 21]. Sensitivity analysis was conducted by two ways: (1) leave-one-out the outlier studies from each outcome; and (2) excluding all outlier studies simultaneously. A brief description for subgroup and network meta-regression analyses are provided in the Supplemental Methods. The rank probability of each treatment in network meta-analysis were presented in surface under the cumulative ranking curve (SUCRA) value [22]. SUCRA are reported in percentages (0-100%) and represent the relative probability of an intervention being one of the best options in the network. We also applying the Confidence in Network Meta-Analysis (CINeMA) to assess the confidence of network estimates with regards to the comparators [23–25]. Meta-proportion was performed using generalized linear mixed models (GLMM) methods [26]. Meta-analyses of proportions focus on estimating the overall (median or population-averaged) proportion, regardless of the transformation used; in this sense, they differ from meta-analyses of treatment comparisons, which may aim at estimating different relative effects (e.g., odds ratio, risk ratio or risk difference), depending on how event rates are transformed [27, 28].

Results

Overview of the study selection process

The PRISMA flow diagram of the entire study selection process is depicted in Fig. 1. The initial database search across six databases yielded a total of 3951 records. From this records, 1324 studies were identified as ineligible by the automation tools, consisting of non-article (*n* = 1166) and comparing anti-arrhythmic agents (*n* = 158). The remaining studies than examined and we found another 932 duplicate studies. Afterwards, 1126 and 237 studies were excluded based on the article title and abstract, respectively. Subsequently, we identified two letter to editors, 17 trial register, 43 conference abstracts, and 13 articles with non-available full text. Lastly, we conducted a comprehensive examination of the full-text of the remaining 257 studies, resulting in the exclusion of 219 studies by the following reasons: inappropriate population (*n* = 7), not intervening with ablation (*n* = 8), comparing to drug therapy (*n* = 14), comparing the strategies or using single modality (*n* = 101), comparing with another modified surgery (*n* = 14), no outcome of interest (*n* = 15), non-randomized study (*n* = 23), wrong study type (*n* = 25), close protocol (*n* = 2), and sub-analysis study (*n* = 10). In addition, we identified additional 130 records from the reference list search, of which 71 studies were duplicates. After going several screening steps, we exclude another 62 studies for reasons outlined in Fig. 1. Finally, we successfully included 46 RCTs in this systematic review and network meta-analysis.

Characteristics and baseline data of included studies

The inclusion and exclusion criteria for each included studies are shown in Table S4. The full description of the specific ablation procedure and characteristics from included studies are presented in Table S5 and Table S6, respectively. MACPAF trial [29] and Chernyavskiy, 2016 [30] were sub-analyses study. These two studies were included due to reported safety outcomes that were not reported in the main study. The included studies yielded nine modalities of ablation, consisting of LPLD radiofrequency (*n* = 35), cryoballoon (*n* = 21), HPSD radiofrequency (*n* = 7), vHPSD radiofrequency (*n* = 3), laser balloon (*n* = 2), microwave (*n* = 1), MIPI (*n* = 4), VATS (*n* = 9), and hybrid (*n* = 4). This study also included a total of 6332 atrial fibrillation patients, of which 1998 were female, representing 31.54% of the study population. The study sample size ranged from 22 to 750 patients with average of the participants aged 60.27. Almost half of included studies were conducted in Europe (*n* = 18), while other studies were conducted in Asia (*n* = 8), America

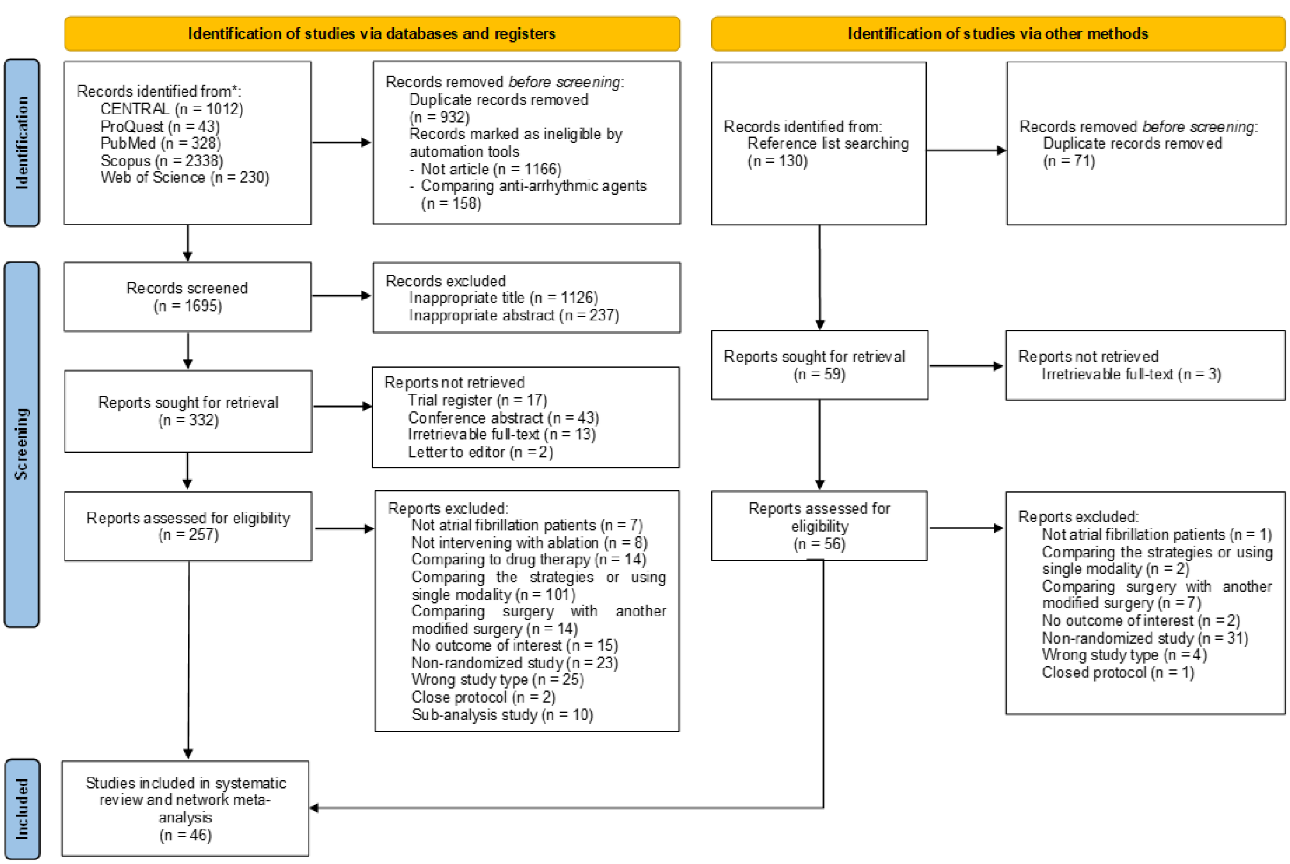


Fig. 1 PRISMA Flow Diagram of the Study Selection Process. CENTRAL, Cochrane Central Register of Controlled Trials

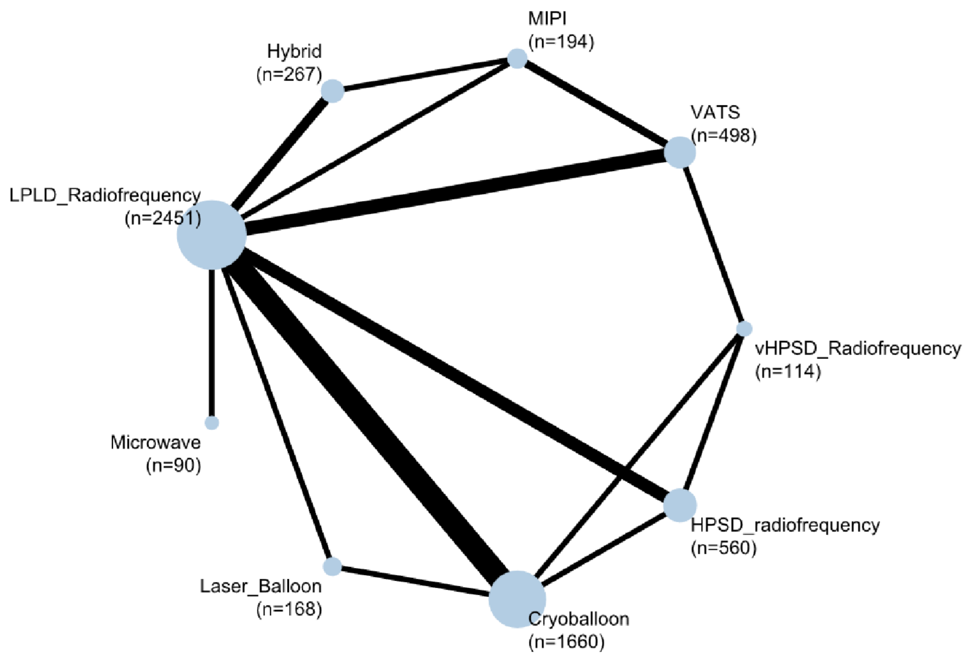


Fig. 2 Network of Eligible Comparisons Plot. LPLD, low power long duration; HPSD, high power short duration; vHPSD, very high power short duration; MIPI, minimally invasive thoracoscopic epicardial pulmonary vein isolation; VATS, video-assisted thoracoscopic surgery

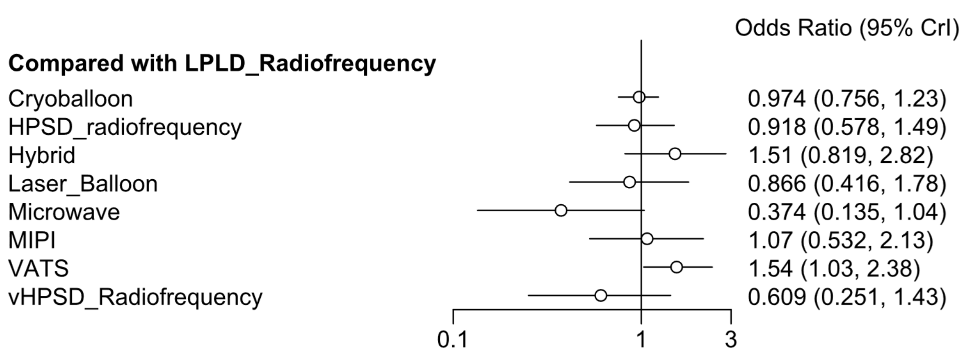


Fig. 3 Forest Plot of Relative Effect from Bayesian Random-Effects Model. LPLD, low power long duration; HPSD, high power short duration; vHPSD, very high power short duration; MIPI, minimally invasive thoracoscopic epicardial pulmonary vein isolation; VATS, video-assisted thoracoscopic surgery; CrI, credible interval

($n = 4$), and Australia ($n = 1$). The included studies have excellent level of adherence rate, with an average of 95.95. For that reason, most of the included studies performed intention-to-treat (ITT) analysis ($n = 34$). Table S7 presented patients baseline characteristics data from each included studies, including AF duration ($n = 26$), LA size ($n = 38$), hypertension proportion ($n = 42$), and procedural time ($n = 39$). We also include the rhythm assessment tool for assessing the outcome at the follow up, which reported by all studies ($n = 46$).

Quality assessment of included studies

The quality assessment utilizing Cochrane's RoB-2 tool found 22,21, and three studies had low, moderate, and high overall risk of bias. The results of domain-specific results are depicted in Figure S2 and detailed quality assessment summary are summarized in Figure S3.

Network meta-analysis

The established network graph plots for each comparisons in this network meta-analysis are depicted in Fig. 2 which analyzed from 43 studies. The forest plot of Bayesian network meta-analysis employs LPLD radiofrequency as the reference treatment (Fig. 3). The detailed results of each individual study were grouped by treatment comparison can be seen in Figure S4. The forest plot demonstrated that patients undergoing VATS (OR 1.54; 95% CrI [1.03, 2.38]; SUCRA 89.61) exhibited a significantly higher freedom from AF compared to those receiving radiofrequency LPLD. Another surgical ablation technique, MIPI, also demonstrated a higher freedom from

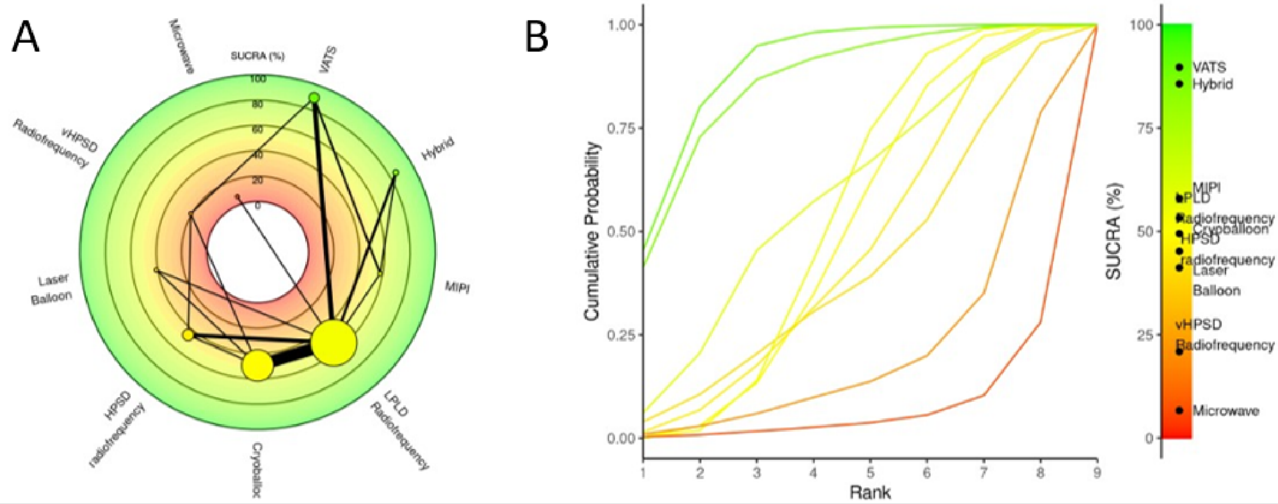
AF rate than radiofrequency LPLD although not significant (OR 1.07; [0.53, 2.13]; 57.59). On the other hand, hybrid ablation (OR 1.51; [0.82, 2.82]; 85.7) exhibited a freedom from AF rate that was comparable to VATS, although the results were not statistically significant. Regarding to catheter ablation modalities, Fig. 4 which presents the league table of Bayesian NMA, indicates that cryoballoon (OR 0.97; [0.75, 1.23]; 49.60), radiofrequency HPSD (OR 0.91; [0.57, 1.49]; 45.11), laser balloon (OR 0.86; [0.41, 1.78]; 41.74), vHPSD radiofrequency (OR 0.61; [0.25, 1.43]; 21.09), and microwave (OR 0.37; [0.13, 1.04]; 6.33) have lower freedom from AF than LPLD radiofrequency. This is evidenced by the SUCRA value, which is presented in the form of Litmus rank-o-gram and radial SUCRA plot (Fig. 5). SUCRA value demonstrated that radiofrequency LPLD exhibited a higher SUCRA value in comparison to other catheter ablation modalities, which is 53.18. Regarding the publication bias, the funnel plot demonstrates a symmetrical distribution, indicating no potential of publication bias within this network meta-analysis (Fig. 6). The results also validated by non-significant Egger's test results ($p=0.278$). Low level of heterogeneity also found in most of the comparisons within this network meta-analysis (Table S8). However, we found moderate to high heterogeneity in hybrid: MIPI ($I^2=52.028\%$), LPLD RF: MIPI ($I^2=76.366\%$), and LPLD RF: VATS ($I^2=62.241\%$). The nodesplit model revealed non-significant inconsistency in all comparisons, which presented in Fig. 7. Global inconsistency assessment also revealed a lower DIC ($DIC_{consistency}$ = 149.584; DIC_{ume} = 154.279).

Sensitivity, subgroup, and network Meta-Regression analysis

The residual deviance values for each arm in each included studies for the network meta-analysis presented in Figure S5 and Table S9. The residual deviance values revealed that five studies [31–35] are identified as outliers in this network meta-analysis. Based on the leave-one-out sensitivity analysis by excluding each outlier, FAST trial [32], Hi-Lo HEAT trial [33], and Pokushalov, 2013.1 [34] found to affect the pooled effect size of the network meta-analysis. Furthermore, the outliers were found to affect the results of network meta-analysis through leave-one-out sensitivity analysis by excluding all outliers simultaneously (Table S10). The results of subgroup analysis for this network meta-analysis were summarized in Table 2. Subgroup analyses found no statistical difference in most of variables, including type of analysis, length of follow-up, type of procedure, blanking period, study location, outcome collection point, and Risk of Bias result. However, different type of AF (β -0.415; 95% CrI [-0.776; -0.042]) found to be influence the results of the network meta-analysis. Therefore, the difference between forest plot of network meta-analysis comparing the paroxysmal and non-paroxysmal AF is depicted in Table S11. Network meta-regression analysis revealed that difference on AF duration (β 0.602; 95% CrI [0.066; 1.079]) had impact to freedom from AF rate. Nevertheless, the network meta-regression results in other covariates demonstrated no significant findings, indicating that there were no additional effect modifiers within this network meta-analysis (Table 3).

Cryoballoon	-0.059 (-0.542, 0.468)	0.438 (-0.208, 1.12)	-0.116 (-0.843, 0.613)	0.025 (-0.208, 0.279)	-0.955 (-1.99, 0.100)	0.095 (-0.631, 0.830)	0.459 (0.002, 0.970)	-0.469 (-1.354, 0.400)
0.059 (-0.468, 0.542)	HPSD radiofrequency	0.495 (-0.290, 1.276)	-0.058 (-0.929, 0.780)	0.085 (-0.401, 0.547)	-0.894 (-2.036, 0.223)	0.153 (-0.697, 0.981)	0.516 (-0.097, 1.144)	-0.411 (-1.291, 0.419)
-0.438 (-1.121, 0.208)	-0.495 (-1.276, 0.290)	Hybrid	-0.554 (-1.524, 0.390)	-0.412 (-1.035, 0.200)	-1.392 (-2.597, -0.203)	-0.339 (-1.065, 0.348)	0.021 (-0.682, 0.732)	-0.910 (-1.996, 0.141)
0.116 (-0.613, 0.843)	0.058 (-0.780, 0.929)	0.554 (-0.390, 1.524)	Laser Balloon	0.143 (-0.579, 0.876)	-0.838 (-2.086, 0.422)	0.206 (-0.786, 1.219)	0.574 (-0.228, 1.440)	-0.351 (-1.493, 0.768)
-0.025 (-0.279, 0.208)	-0.085 (-0.547, 0.401)	0.412 (-0.200, 1.035)	-0.143 (-0.876, 0.579)	LPLD Radiofrequency	-0.982 (-2.005, 0.034)	0.070 (-0.631, 0.758)	**0.432 (0.029, 0.868)**	-0.495 (-1.380, 0.358)
0.955 (-0.100, 1.996)	0.894 (-0.223, 2.036)	1.392 (0.203, 2.597)	0.838 (-0.422, 2.086)	0.982 (-0.034, 2.005)	Microwave	1.050 (-0.194, 2.277)	1.414 (0.334, 2.538)	0.485 (-0.875, 1.807)
-0.095 (-0.830, 0.631)	-0.153 (-0.981, 0.697)	0.339 (-0.348, 1.065)	-0.206 (-1.219, 0.786)	-0.070 (-0.758, 0.631)	-1.050 (-2.277, 0.194)	MIPI	0.363 (-0.340, 1.105)	-0.567 (-1.673, 0.531)
-0.459 (-0.970, -0.002)	-0.516 (-1.144, 0.097)	-0.021 (-0.732, 0.682)	-0.574 (-1.440, 0.228)	**-0.432 (-0.868, -0.029)**	-1.414 (-2.538, -0.334)	-0.363 (-1.105, 0.340)	VATS	-0.929 (-1.890, -0.018)
0.469 (-0.400, 1.354)	0.411 (-0.419, 1.291)	0.910 (-0.141, 1.996)	0.351 (-0.768, 1.493)	0.495 (-0.358, 1.380)	-0.485 (-1.807, 0.875)	0.567 (-0.531, 1.673)	0.929 (0.018, 1.890)	vHPSD Radiofrequency

Fig. 4 League Table of Freedom from AF Network Meta-Analysis. Comparison should be read from left to right. Outcomes estimates are located at the intersection between the column-defining treatment and the row-defining treatment. Data are presented as Odds Ratio (95% CrI). Data higher 1 favour for freedom from AF outcome. Treatments are reported in alphabetical orders while control reported in the middle order. LPLD, low power long duration; HPSD, high power short duration; vHPSD, very high power short duration; MIPI, minimally invasive thoracoscopic epicardial pulmonary vein isolation; VATS, video-assisted thoracoscopic surgery



Treatment	SUCRA
VATS	**89.616**
Hybrid	85.701
MIPI	57.598
LPLD_Radiofrequency	53.186
Cryoballoon	49.609
HPSD_radiofrequency	45.116
Laser_Balloon	41.748
vHPSD_Radiofrequency	21.091
Microwave	6.335

Fig. 5 Radial SUCRA Plot (**A**) and Litmus Rank-O-Gram Plot (**B**) Summarized SUCRA Value for Network Meta-Analysis. Higher SUCRA (Surface Under the Cumulative Ranking Curve) values indicate better treatments. Radial SUCRA Plot: The size of nodes represent the number of participants, and the thickness of lines indicate the number of trials conducted. Litmus Rank-O-Gram: Cumulative ranking curves nearer the top left indicate better performance. LPLD, low power long duration; HPSD, high power short duration; vHPSD, very high power short duration; MIPI, minimally invasive thoracoscopic epicardial pulmonary vein isolation; VATS, video-assisted thoracoscopic surgery

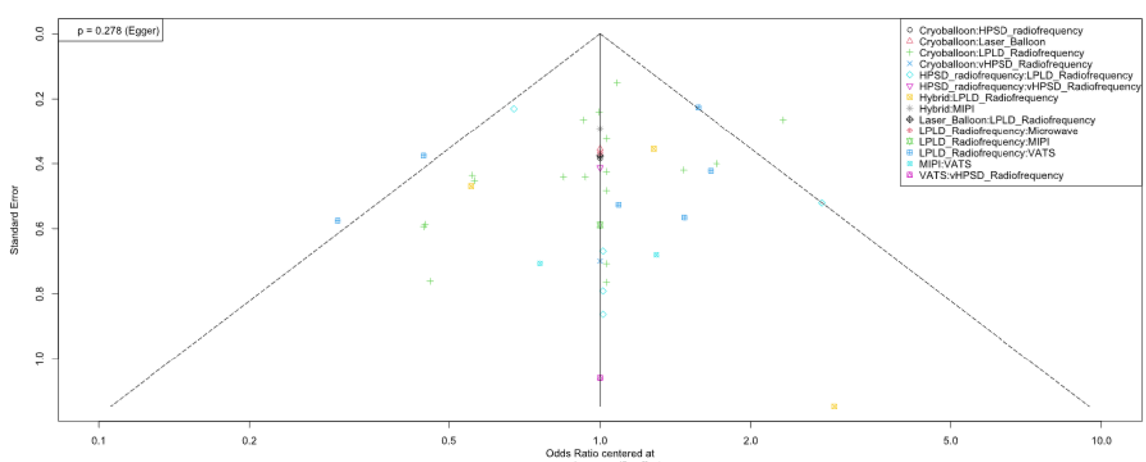


Fig. 6 Funnel Plot for Freedom from AF Network Meta-Analysis. LPLD, low power long duration; HPSD, high power short duration; vHPSD, very high power short duration; MIPI, minimally invasive thoracoscopic epicardial pulmonary vein isolation; VATS, video-assisted thoracoscopic surgery

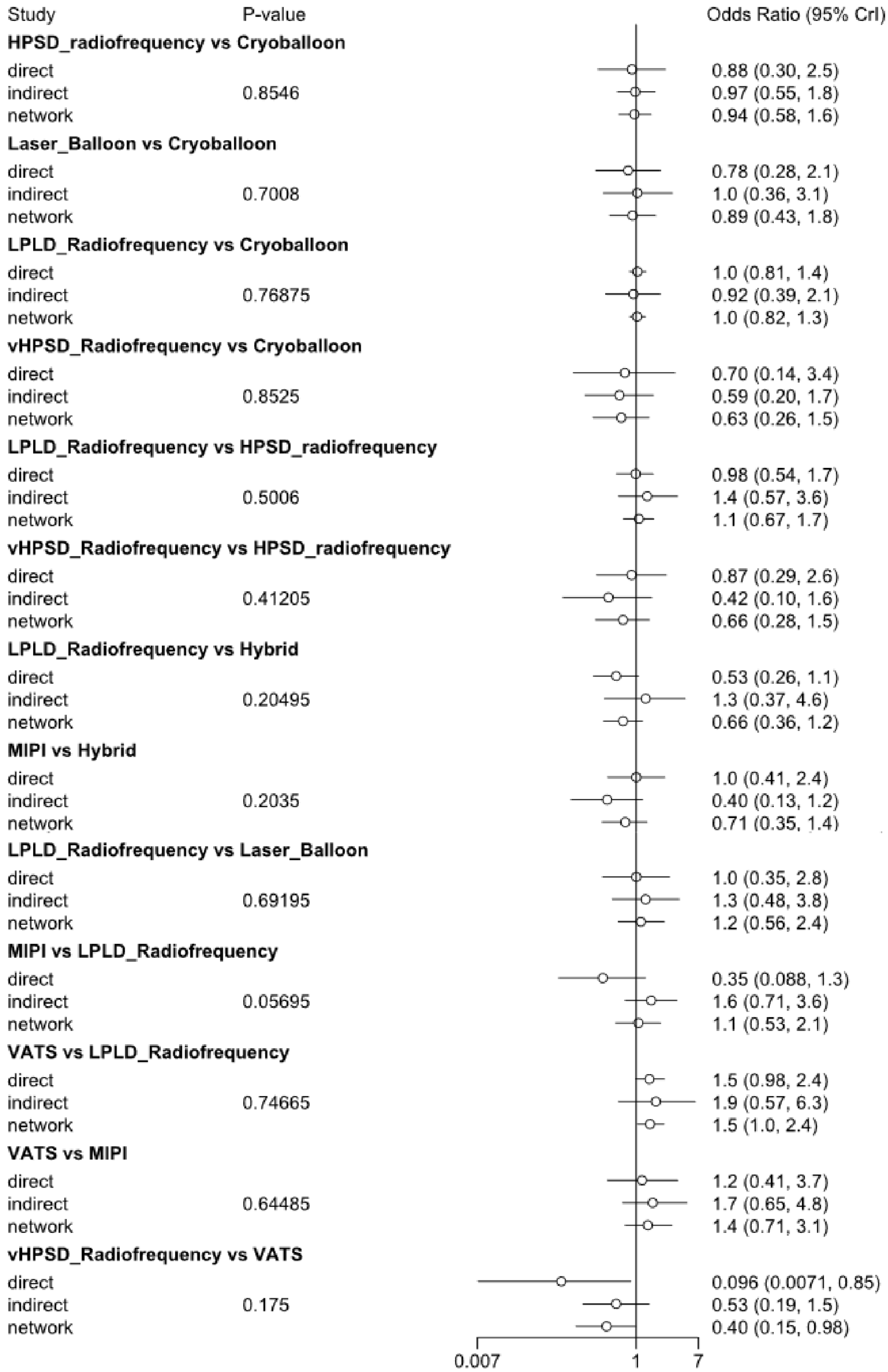


Fig. 7 Forest Plot of Nodesplit Model for Freedom from AF Network Meta-Analysis. The direct and indirect components of the evidence are reported along with the combined evidence and the *p*-value for the inconsistency. CrI, credible interval; LPLD, low power long duration; HPSD, high power short duration; vHPSD, very high power short duration; MIPI, minimally invasive thoracoscopic epicardial pulmonary vein isolation; VATS, video-assisted thoracoscopic surgery

Table 2 Subgroup analyses for network Meta-Analysis of freedom from AF

Outcome measure	Variable	Subgroup	β	Lower 95% CrI	Upper 95% CrI	Significancy
Freedom from AF	**Type of Analysis**	ITT	0.026	-0.449	0.461	Not Significant
		PP				
	Atrial Fibrillation type	Paroxysmal	-0.415	-0.776	-0.042	**Significant**
		Non-Paroxysmal				
	Length of Follow Up	=< 12 months	0.095	-0.736	0.938	Not significant
		> 12 months				
	Type of Procedure	Left atrial	-0.057	-0.565	0.439	Not significant
		Bi-atrial				
	Blanking Period	3 months	0.141	-0.709	0.991	Not significant
		Non-3 months				
	Study Location	Europe	0.373	-0.121	0.869	Not significant
		Non-Europe				
	Outcome Collection Point	12 months	-0.062	-0.729	0.581	Not significant
		non-12 months				
	RoB	Low risk	0.167	-0.227	0.615	Not significant
		Some concerns and High risk				

ITT, intention-to-treat; **PP**, per protocol; **RoB**, risk of bias; **β**, Beta Coefficient; **AF**, atrial fibrillation; **CrI**, credible interval

Table 3 Summary of network Meta-Regression analysis on freedom from AF network Meta-Analysis

Outcome measure	Covariate	β	Lower 95% CrI	Upper 95% CrI	Interpretation
Freedom from AF	**Sample size**	0.004	-0.291	0.317	Not significant
	Adherence	-0.077	-0.515	0.341	Not significant
	AF duration	0.602	0.066	1.079	**Significant**
	Age	0.502	-0.081	1.107	Not significant
	Gender Distribution	-0.135	-0.561	0.011	Not significant
	Hypertension Proportion	-0.496	-0.069	0.382	Not significant
	LA size	0.09	-0.573	0.72	Not significant

β, Beta Coefficient; **AF**, atrial fibrillation; **LA**, left atrial; **CrI**, credible interval

Quality of evidence

The within-study bias assessment revealed a majority of no concerns regarding bias with the comparisons in the network, as outlined in Figure S6. The GRADE report also evaluated the contribution of indirectness of the network, as depicted in Figure S7. Lastly, GRADE report also identified significant imprecision and heterogeneity, which downgrade the confidence rating level (refer to Figure S8).

Adverse effect

As evidenced in Table 4, patients who have undergone catheter ablation, particularly those who have received LPLD radiofrequency, are at an elevated risk for developing atrial flutter/tachycardia (prop = 9.75; 95% CI [4.94; 18.31]) and pneumonia (prop = 4.17; 95% CI [0.00; 97.79]). Conversely, pericardial effusion represented the primary concern associated with the utilization of vHPSD radiofrequency (prop = 6.67; 95% CI [0.93; 35.2]). Patients who received cryoballoon intervention were also found to be at risk for transient ST elevation (prop = 5.88; 95% CI [0.82; 32.03]). Similar to LPLD radiofrequency, patients who have undergone laser balloon intervention are at risk of developing atrial flutter/tachycardia (prop = 7.8; 95% CI [0.31; 69.83]) and transient ST elevation (prop = 5.71; 95% CI [1.43; 20.16]).

Table 5 summarizes the results of meta-proportions on adverse effects from surgical and hybrid ablation modalities. The meta-proportion results indicated that patients who underwent surgical or hybrid ablation exhibited a heightened risk of complications relative to those who underwent catheter ablation. This is evidenced by the mortality rate of patients undergoing VATS, which is 5.07%. Conversely, patients who received MIPI will have a risk of pericardial effusion and phrenic nerve injury of 4.35%. Despite the higher complication rate in patients undergoing surgical and hybrid ablation, the side effects observed in these patients are less diverse than those seen in patients undergoing catheter ablation.

Discussion

Main findings

Based on the SUCRA values and the result of the current NMA, we found that AF ablation using VATS is the most effective strategy in terms of achieving freedom from AF events, followed by hybrid ablation, MIPI, LPLD RF, cryoballoon, HPSD RF, laser balloon, vHPSD RF, and microwave ablation. In general, there are two approaches for conducting AF ablation, which are endocardial and epicardial. In this study arms, RF, cryoballoon, laser balloon, and microwave are modalities grouped into the endocardial ablation approach, while VATS and MIPI are surgical ablation techniques that uses the epicardial

Table 4 Summary of Meta-Proportions on adverse effects from different modalitites of catheter ablation

Adverse Effects	LPLD Radiofrequency			HPSD Radiofrequency			vHPSD Radiofrequency			Cryoballoon			Laser Balloon		
	k	Prop	95% CI	k	Prop	95% CI	k	Prop	95% CI	k	Prop	95% CI	k	Prop	95% CI
Anaphylactic shock	1	0	0.00; 1.00	-	-	-	-	-	-	-	-	-	-	-	-
Arteriovenous fistula	3	1.68	0.00; 27.58	2	0	0.00; 1.00	-	-	-	-	-	-	-	-	-
Atrial flutter / tachycardia	8	9.75	4.94; 18.31	1	0	0.00; 1.00	1	0	0.00; 1.00	4	1.56	0.60; 3.99	2	7.8	0.31; 69.83
Atrioesophageal fistula	3	0	0.00; 1.00	-	-	-	-	-	-	1	0	0.00; 1.00	1	0	0.00; 1.00
Cardiac tamponade	14	1.15	0.71; 1.86	5	0.44	0.14; 1.34	2	0.83	0.00; 1.00	3	0.26	0.01; 5.23	2	0.84	0.00; 98.6
Chest infection	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Death	9	0.32	0.03; 3.82	1	0		1	0	0.00; 1.00	1	0.53	0.13; 2.11	2	0	0.00; 1.00
Diaphragm paralysis	4	0.47	0.05; 4.31	-	-	-	-	-	-	-	-	-	1	3.53	1.59; 7.63
Femoral pseudoaneurysm	5	1.05	0.26; 4.11	1	0.58	0.08; 3.99	-	-	-	-	-	-	-	-	-
Groin hematoma/bleed	13	2.41	1.30; 4.44	4	0.6	0.20; 1.84	2	0	0.00; 1.00	6	3.21	0.96; 10.22	1	0	0.00; 1.00
Heart failure	4	0.77	0.1; 5.51	2	0.5	0.00; 47.57	-	-	-	-	-	-	-	-	-
Myocardial infarction	4	0.32	0.01; 7.25	-	-	-	-	-	-	-	-	-	2	0.41	0.00; 99.99
Pericardial effusion	5	1.07	0.31; 3.62	-	-	-	1	6.67	0.93; 35.2	4	0.71	0.11; 4.34	-	-	-
Phrenic nerve injury	8	0.09	0.01; 0.99	2	0.47	0.00; 58.35	-	-	-	11	4.14	2.92; 5.83	3	1.97	0.23; 15.1
Pneumonia	2	4.17	0.00; 97.79	1	0	0.00; 1.00	-	-	-	-	-	-	-	-	-
Postinterventional pericarditis	-	-	-	4	1.42	0.12; 14.70	-	-	-	-	-	-	1	2.86	0.40; 17.69
PV stenosis	9	0.47	0.08; 2.82	2	0.38	0.00; 99.92	1	0	0.00; 1.00	1	0	0.00; 1.00	1	0	0.00; 1.00
Sepsis, abscesses, or endocarditis	8	0.70	0.09; 5.48	1	3.23	0.45; 19.64	-	-	-	1	0.75	0.11; 5.14	1	2.86	0.4; 17.69
Stroke	11	0.44	0.18; 1.10	3	0.09	0.00; 6.02	1	0	0.00; 1.00	1	0.56	0.05; 6.33	3	1.83	0.27; 11.51
Transient ST elevation	-	-	-	1	0	0.00; 1.00	-	-	-	1	5.88	0.82; 32.03	1	5.71	1.43; 20.16
TIA	8	0.77	0.32; 1.87	-	-	-	-	-	-	3	0.18	0.00; 11.77	2	0.37	0.00; 99.92

LPLD, low power long duration; **HPSD**, high power short duration; **vHPSD**, very high power short duration

Table 5 Summary of Meta-Proportions on adverse effects from different modalitites of surgical and hybrid ablation

Adverse Effects	VATS			MIPI			Hybrid		
	k	**Prop**	**95% CI**	**k**	**Prop**	**95% CI**	**k**	**Prop**	**95% CI**
Anaphylactic shock	1	1.82	0.26; 11.81	-	-	-	-	-	-
Arteriovenous fistula	-	-	-	-	-	-	-	-	-
Atrial flutter / tachycardia	1	3.13	0.44; 19.11	-	-	-	1	2	0.28; 12.88
Atrioesophageal fistula	-	-	-	-	-	-	1	0	0.00; 1.00
Cardiac tamponade	1	3.13	0.44; 19.11	-	-	-	2	3.31	0.01; 95.63
Chest infection	-	-	-	1	3.64	0.91; 13.41	-	-	-
Death	3	5.07	1.00; 22.09	3	0	0.00; 1.00	1	0	0.00; 1.00
Diaphragm paralysis	-	-	-	-	-	-	-	-	-
Femoral pseudoaneurysm	2	0	0.00; 1.00	-	-	-	1	5.26	0.74; 29.39
Groin hematoma/bleed	2	0	0.00; 1.00	2	0	0.00; 1.00	2	1.65	0.00; 99.31
Heart failure	1	1.67	0.23; 10.9	2	0	0.00; 1.00	-	-	-
Myocardial infarction	-	-	-	-	-	-	2	0	0.00; 1.00
Pericardial effusion	1	1.89	0.27; 12.21	1	4.35	0.61; 25.22	-	-	-
Phrenic nerve injury	-	-	-	1	4.35	0.61; 25.22	1	0.98	0.14; 6.63
Pneumonia	1	5.66	1.84; 16.13	1	3.28	0.82; 12.18	-	-	-
pneumothorax	1	9.37	3.06; 25.35	-	-	-	-	-	-
Postinterventional pericarditis	-	-	-	1	1.64	0.23; 10.73	-	-	-
PV stenosis	-	-	-	2	0	0.00; 1.00	2	0	0.00; 1.00
Sepsis, abscesses, or endocarditis	3	5.47	1.07; 23.55	1	1.64	0.23; 10.73	1	5.26	0.74; 29.39
Stroke	1	1.89	0.27; 12.21	3	0	0.00; 1.00	1	0	0.00; 1.00
Transient ST elevation	-	-	-	-	-	-	-	-	-
TIA	1	0	0.00; 1.00	3	0	0.00; 1.00	1	0.98	0.14; 6.63

MIPI, minimally invasive thoracoscopic epicardial pulmonary vein isolation; **VATS**, video-assisted thoracoscopic surgery

approach. Most recently, hybrid techniques combining both endocardial and epicardial approach have been developed [36].

Endocardial catheter approach using radiofrequency catheter was the first developed technique for AF ablation, and several other energy modalities have been used to date. As their names indicate, RF, cryoballoon, laser balloon, and microwave ablation each uses different types of energy targeted to the cardiac tissue. However, data showed high recurrences of AF after endocardial ablation that require repeated ablation procedures. Accordingly, due to the recognition of patients with risk factors for poor outcomes using a standard endocardial ablation, surgical epicardial approach was later developed as an alternative technique to improve efficacy [36]. This evidence is confirmed by our study, where techniques that incorporated epicardial approach (i.e., hybrid ablation, VATS, and MIPI) are superior to that using endocardial approach regarding freedom from AF events.

A previous NMA by Tokavanich et al. (2023) have studied different RF powers for AF ablation [37]. The result of the study is in line with the current finding, in which vHPSD ablation is not superior to HPSD and LPLD, or also referred to as conventional power. Another NMA by Kukendrarajah et al. (2020) comparing cryoballoon, RF, and laser Endo catheter AF ablation showed comparable efficacy for achieving freedom from AF events, which is similar to the findings of our studies [38]. We found an interesting finding, where patients treated with VATS, an epicardial-only approach, had a lower risk of AF recurrence compared to hybrid strategy. In theory, hybrid strategy is likely to be more efficacious, since it yields the advantage of both surgical and catheter-based ablation [36]. In 2022, Charitakis et al. have attempted to compare different catheter ablation strategies, including PVI alone and PVI with autonomic modulation and additional lines, through NMA, and they found that the additional modification to PVI decreases the risk of AF recurrence compared to PVI alone [39]. Our included studies that used VATS and hybrid strategy performed different types of ablation line and set, which may affect the procedure outcomes. Overall, this evidence suggests that ablation approach, modalities, and lines are crucial factors for determining the most effective strategies for the management of AF.

Sensitivity analysis using the residual deviance value revealed five studies that considered as outliers. Differences between sites in several of the practical procedural details in both groups may be the reasons for this event, which also stated in the study. Subgroup analysis found that the sub-analyses on atrial fibrillation type revealed a significant difference on incidence of freedom from AF. The result demonstrate that ablation is more effective in patients with non-paroxysmal atrial fibrillation than in patients with paroxysmal atrial fibrillation in terms of freedom from AF cases. Network meta-regression notable a significant difference in the AF duration covariate, while other covariates, such as age, gender distribution, and hypertension proportion showed no significant differences. Network meta-regression indicate that patients with longer AF duration demonstrate a higher rate of freedom from AF than patients with shorter AF duration. The result is consistent between network meta-regression and subgroup analysis, as duration of AF also used to categorize the types of AF. However, current evidence shows that catheter ablation is generally more effective paroxysmal AF compared to non-paroxysmal AF, in terms of sinus rhythm (SR) maintenance [40]. The underlying reason for this phenomenon is that the primary triggers of paroxysmal AF are often located in the pulmonary veins, making pulmonary vein isolation (PVI) a highly effective treatment strategy [41, 42]. In contrast, in non-paroxysmal AF, the arrhythmia is frequently sustained by non-PV triggers and complex atrial substrates, providing additional ablation techniques beyond PVI [40, 43]. This also addresses our findings, where some studies also performed ablation on additional lesion sets which may lead to increased freedom from AF in non-paroxysmal AF patients.

The pooled prevalence of AEs in our study can be seen from two opposite sides. First, based on the approach type, ablation involving epicardial approach (VATS, MIPI, and hybrid) shows higher pooled prevalence of AEs than ablation involving only endocardial approach (radiofrequency, cryoballoon, and laser balloon). Previous meta-analysis with mixed study designs states that epicardial ablation through surgical approach also has a higher tendency to have AEs, including pacemaker implantation and stroke / transient ischemic attack (TIA), than endocardial catheter ablation [44]. Furthermore, thoracoscopic ablation has approximately 4 to 7 times higher risk of having significant AEs than catheter ablation, especially during periprocedural period [45]. This finding is still consistent for hybrid ablation with almost three times higher rates of having procedural-related AEs than endocardial catheter ablation [46]. These findings can be explained by the fact that epicardial ablation carries some important limitations: (1) it carries significant anatomic variations that differ from one patient to another and (2) it is an operator-dependent approach, which depends on the comfort level, skill, and experience of the cardiac surgeon [36]. However, even though epicardial approach has a higher rate of AEs than endocardial approach in our study, the number of AEs in each included study is still poorly reported, indicating that the AEs are still generally rare across those studies, as also described by the previous meta-analysis [44].

Second, based on the listed AEs, ablation that involves endocardial approach (radiofrequency, cryoballoon, and laser balloon) shows more diverse AEs compared to ablation that involves epicardial approach (VATS, MIPI, and hybrid). Previous review also shows a broad spectrum of complications in endocardial approach [47]. This might be explained by two reasons: (1) the need of repeated ablation in some cases and (2) the various types of modalities and ablation sets used in the endocardial approach [47, 48]. Several modalities, such as cryoballoon and laser balloon, need a shorter learning curve, are less operator-dependent, and are more suitable for centers with limited experience in AF ablation than other modalities, especially radiofrequency [47]. This pattern is also seen in our findings, which reveal less diverse of AEs in both modalities compared to radiofrequency. Moreover, the ablation sets are also possible to be involved in the development of broad spectrum of AEs. The most commonly used ablation set is PVI. The AEs of this approach really depend on the operator's experience, the skills in anatomical approach, and the anatomic variants of the pulmonary vein [49, 50]. One of the latest developed techniques to prevent those errors in PVI is complex fractionated atrial electrograms (CFAE), which incorporates new technologies to better visualize the specific AF-culprit substrate in the atrial wall [48]. This technique might reduce the spectrum and the number of AEs in endocardial ablation approach.

Strength and limitation

To the best of the author's knowledge, this study is the first systematic review and network meta-analysis to assess both the effectiveness and safety of disparate ablation modalities strategies in patients with atrial fibrillation. The included studies encompass a global scope, including Asia, America, Australia, and Europe, and comprise a sufficient number of samples within the network meta-analysis, which will enhance the study's findings. Moreover, the inconsistency analysis through global and local approaches also revealed that no potential effect modifier exists within this network meta-analysis.

Despite the authors' best efforts to ensure the highest possible quality of the study, we acknowledged some areas for improvement. First, although this study analyzes the comparison of modalities used for ablation, different types of ablation lines and sets may also influence the outcomes of the procedure. Second, while we have made every effort to extract all available data on AEs, the number of studies reporting AE occurrences remains limited. Third, the experience of surgeons performing both epicardial and endocardial procedures is an uncontrolled factor in this study and may have influenced the results. Fourth, another modality, pulse-field ablation, has recently gained attention. However, the number of RCTs on this modality remains very limited. Study by Reddy et al. 2023 [51] compared pulse-field ablation with thermal ablation (radiofrequency and cryoablation).

Since the control group did not distinguish between radiofrequency and cryoablation, the comparison lacked balance, potentially introducing inconsistency. Given that only one other study, conducted by Osmancik et al. 2024 [52], we believe that including only a single study to represent a treatment modality carries a risk of overstatement. Therefore, we consider that more RCTs on pulse-field ablation are necessary before it can be included in our NMA. Lastly, some concerns regarding heterogeneity and imprecision evaluation were found, resulting in a downgrade in the confidence rating. However, the cause of this phenomenon was successfully revealed through the sensitivity and network meta-regression analysis.

Conclusion

The NMA reinforce the efficacy of epicardial ablation strategies, particularly VATS and combined epicardial-endocardial (hybrid) approaches, in managing patients with atrial fibrillation. These modalities have been demonstrated to be more effective in reducing the recurrence rate of AF compared to other techniques. Although complications associated with these ablation techniques were observed to have a higher prevalence than those observed with other catheter ablation modalities, the prevalence rates still comparable, and the types of complications encountered are less diverse. The findings require further validation through further studies that specifically examine ablation approaches and line set to determine the optimal use of ablation in patients with AF.

Abbreviations

AE	Adverse effect
AF	Atrial fibrillation
B	Beta coefficient
CA	Catheter ablation
CENTRAL	Cochrane Central Register of Controlled Trials
CF	Contact force
CFAE	Complex fractionated atrial electrograms
CI	Confidence interval
CINeMA	Confidence in Network Meta-Analysis
CrI	Credible interval
DIC	Deviance Information Criterion
GLMM	Generalized linear mixed models
GRADE	Grades of Recommendation, Assessment, Development, and Evaluation
HPSD	High power short duration
ITT	Intention-to-treat
LA	Left atrial
LPLD	Low power long duration
MCMC	Markov Chain Monte Carlo
MeSH	Medical Subject Headings
MIPI	Minimally invasive thoracoscopic epicardial pulmonary vein isolation
NMA	Network meta-analysis
OR	Odds ratio
PICO	Population, Intervention, Comparison, Outcome
PP	Per protocol
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
Prop	Proportion
PROSPERO	International prospective register of systematic reviews
PSRF	Potential Scale Reduction Factor
PVI	Pulmonary vein isolation
RCT	Randomized Controlled Trial
RF	Radiofrequency
RoB-2	Cochrane Collaborations' Risk of Bias 2 tool
SA	Surgical ablation
SIDE	Separating Indirect from Direct Evidence
SR	Sinus rhythm
SUCRA	Surface under the cumulative ranking curve
TIA	Transient ischemic attack
VATS	Video-assisted thoracoscopic surgery
vHPSD	Very high power short duration

Supplementary Information

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Supplementary Material 1

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Author contributions
FMA: Conception, Design of the work, Acquisition, analysis, Interpretation of data, creation of new software used in the work, drafted the work, revised the work, approved the submitted version, agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature. VV, BSW: Conception, Design of the work, Interpretation of data, drafted the work, approved the submitted version, agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature. APW, JOH: Drafted the work, revised the work, approved the submitted version, agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature. YES, JD: Interpretation of data, Revised the work, approved the submitted version, agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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All the analysis and data will be made available and can be requested through the first author (FMA).

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Competing interests
The authors declare no competing interests.

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